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Indolizine-Squaraine NIR Emissive Materials

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INDOLIZINE-SQUARAINI NIR EMISSIVE MATERIALS

by
Tana Anne Rill

A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of
the requirements of the Sally McDonnell Barksdale Honors College

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ABSTRACT

Near-infrared (NIR) emissive organic materials are an emerging area of study with an array of applications for both military and civilian purposes including night vision technologies, secure communications, surveillance, homing, fluorescence imaging, secure displays as NIR OLED materials, heat-blocking coatings, in vivo fluorescence biological imaging, and additional optoelectronics device applications.

We have developed a series of organic NIR emissive materials based on an indolizine donor and squaraine acceptor. The novel-to-squaraine donor, indolizine, exhibits a remarkable increase in absorption maximum wavelength when compared with benchmark indoline-based squaraine dyes (700 nm vs. 625 nm) with molar absorptivities ranging from 100,000-262,000 $\text{M}^{-1}\text{cm}^{-1}$. Emission is observed at about 750 nm in chloroform, corresponding to a stokes shift of 50 nm, which is a substantial increase when compared with the 5 nm stokes shift commonly observed for indoline-squaraine dyes. Our molecular design was evaluated by computational analysis which reveals clues about the origin of this stokes shift and the water solubility observed for these compounds without appending water solubilizing groups.

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Introduction.

Functional organic dyes have made many significant contributions to the development of electronic and photonic devices recently, particularly in hi-tech photon-based technologies of electronics and optoelectronics. Due to their extremely tunable properties, dyes used in these applications are at the forefront of many emerging technologies. Of particular interest are near-infrared (NIR) emissive organic materials, driven by their applications for both military and civilian purposes. Military applications include night vision technology, secure communications, surveillance, homing, fluorescence imaging, transparent photovoltaics, secure displays and heat-blocking coating.^{1,2,3} Nonmilitary uses for NIR materials involve a number of important sectors, such as energy conversion, in vivo fluorescence bioimaging, sensitizing and optoelectronics.^{4,5}

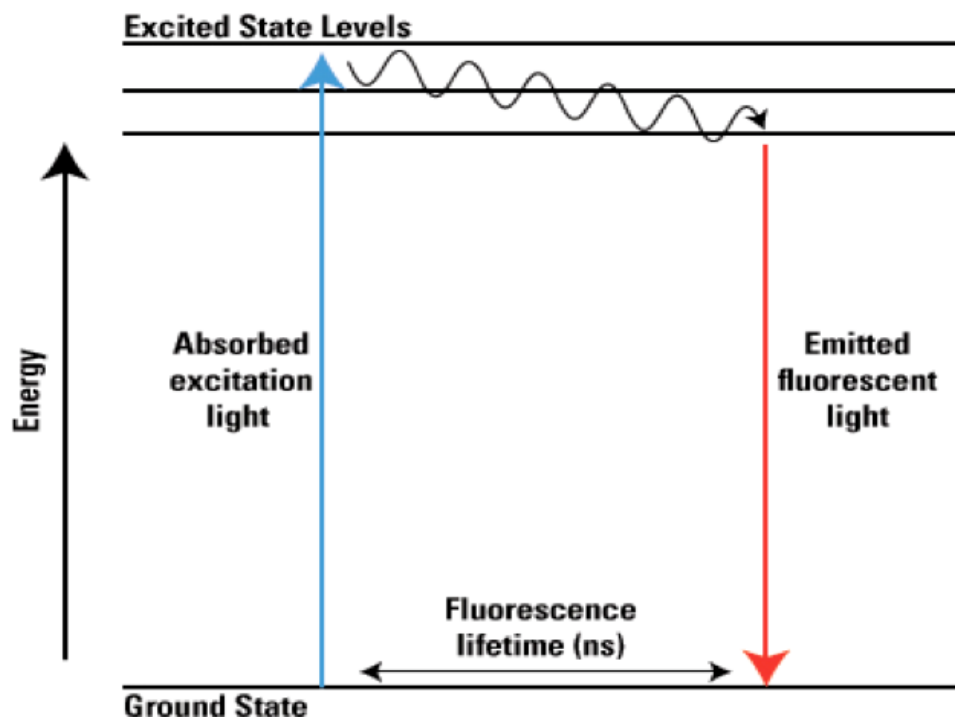


Figure 1. Jablonski diagram of an emissive process.

For many applications, highly emissive materials are desirable. Fluorescence is the luminescence that occurs when energy is supplied by electromagnetic radiation. This can occur when a molecule in an excited state relaxes to its ground state, as illustrated in a Jablonski diagram, shown in *Figure 1*.⁶ *Figure 1* describes the absorption and emission of a molecule, where the blue arrow represents the molecule being irradiated to an excited state, the black arrow represents vibrational relaxation from a higher energy excited state to S_1 , and the red arrow represents either fluorescence or phosphorescence to the singlet ground state, S_0 . There are many other relaxation pathways that a molecule may undergo to give non-radiative decay. The efficiency of fluorescence is described by fluorescence quantum yield (Φ , *Equation 1*), which is a ratio of the photons absorbed resulting in the emission of fluorescence to the total number of photons absorbed rate of fluorescence to the rate of all relaxation pathways that the molecule may undergo.

$$\varphi = \frac{k_f}{k_f + k_{nr}}$$

Equation 1. Fluorescence quantum yield, where k_f is the rate of fluorescence and k_{nr} is the rate of non-radiative decay.

Emissive materials may be further described by the wavelengths (λ) at which the lowest energy maximum light absorption and maximum emission occurs, the difference of which is known as the Stokes shift. When a molecule is excited, it often undergoes conformational changes to become planar and allow free movement of electrons. The molecule will undergo the same conformational changes to move from the completely flat, planar excited state to the “twisted” ground state, increasing the difference between absorption and emission wavelengths and giving a larger Stokes shift. However, the more conformational changes that the molecule undergoes, the longer the relaxation time will

be. The longer relaxation time allows other non-radiative decays to kinetically compete, decreasing the fluorescence quantum yield. These two characteristics must be balanced, because if the Stokes shift is too narrow, emission wavelengths can be difficult to detect over absorption wavelengths for many applications. *Figure 2* illustrates a general absorption and emission spectra with the difference of a Stokes shift indicated.⁷

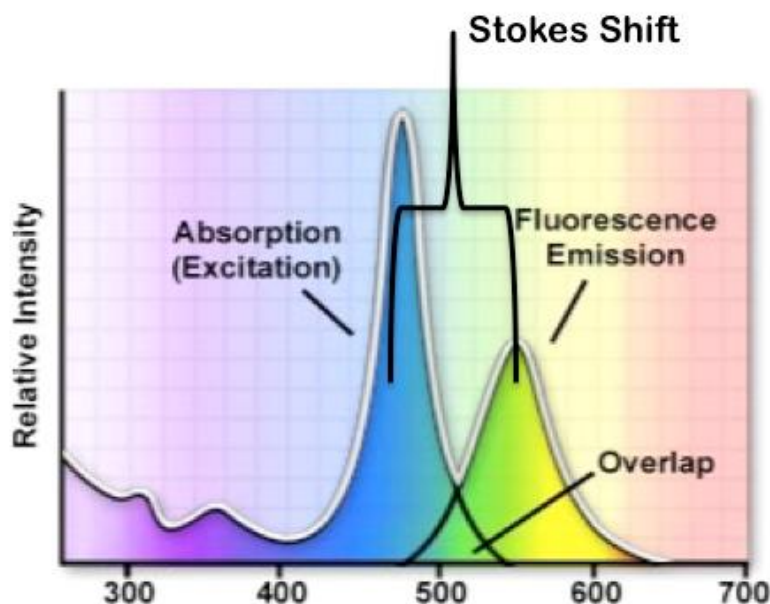


Figure 2. General absorption and emission spectra indicating the Stokes shift of a molecule.

Of particular interest for NIR emissive materials is their application for in-vivo biological imaging, due to low tissue autofluorescence and high tissue light penetration in the NIR spectrum window.^{8,9} Traditional modalities in molecular imaging employ ionizing radiation with low sensitivity and poor resolution.^{10,11} NIR organic emissive molecules provide an option of noninvasive molecular imaging, with high sensitivity to chemical reagent and high target to background ratio, giving better visibility in imaging. One

important parameter for NIR emissive materials in optical imaging is that fluorescence events take place in an imaging window which is suitable to biological systems. This window, referred to as the therapeutic window, ranges from $\lambda = 650\text{-}900\text{ nm}$,^{10,12,13} as seen below in *Figure 3*.¹⁴

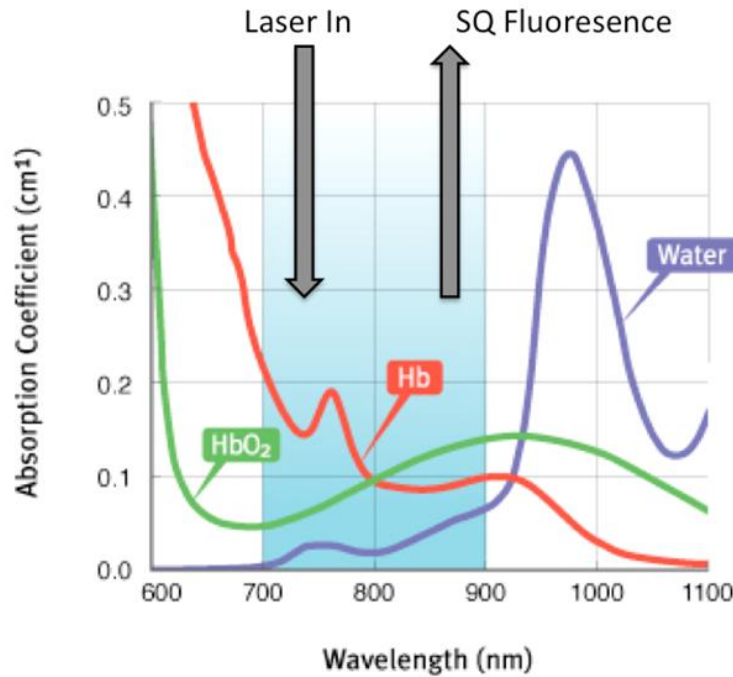


Figure 3. The therapeutic window for NIR emissive materials. HbO₂ is oxygenated hemoglobin and Hb is deoxygenated hemoglobin.

In this range of wavelengths, light absorption from water, melanin, proteins, and hemoglobin within the biological system are at their lowest, as well as minimal tissue autofluorescence occurs, allowing for deep penetration of light.^{15,16} Fluorescent dyes with both absorption and emission within the therapeutic window are extremely desirable, as even molecules with high fluorescence quantum yields that do not absorb and emit light within this spectral range will have severely attenuated signals due to inadequate excitation as a result of poor light penetration depth.

With the right chemical and spectral properties, organic fluorescent dyes are strong candidates for biological imaging agents. This requires that the organic molecules have intrinsic properties fitting to a biological system, including excitation and emission wavelengths within the therapeutic window, a high fluorescence quantum yield and a high absorption coefficient as well as good water solubility, Stokes shift, photostability and chemical stability in different environments. Due to the limitations of many conventional dyes, such as poor hydrophilicity, low quantum yields and insufficient stability, there are few NIR dyes that meet these requirements.¹⁷ The classes of dyes that are widely studied for use in biological imaging include cyanines, phthalocyanines/porphyrin derivatives, BODIPY (borondipyrrolmethane) analogues, and squaraines.¹² Each class has its own general advantages and disadvantages with typical values summarized in *Table 1* below.

Organic Dyes	Absorption range (nm)	Fluorescence emission range (nm)	Photo-stability	Molar extinction coefficient (M⁻¹ cm⁻¹)	Fluorescence quantum yield (Φ)
Cyanines	400-800	500-800	Poor	~200,000	0.12-0.67
Phthalocyanines / Porphyrin derivatives	350-800	350-800	High	~100,000	-
BODIPY analogues	500-645	506-760	Very high	~80,000	0.92
Squaraines	350-900	350-900	High	~300,000	0.1-0.86

Table 1. Emissive organic dyes and general spectral properties.

Cyanine dyes, characterized by two aromatic nitrogen containing heterocycles connected with a polymethine bridge, have been studied extensively, are easily tunable to

the NIR region simply by extension of the methine bridge, and have strong absorption coefficients at about $200,000 \text{ M}^{-1}\text{cm}^{-1}$.^{18,19,20} Most cyanine dyes exhibit low quantum yield (ranging about 1% to 7%), which extension of the polymethine bridge lowers further.²¹ One cyanine dye, known as Indocyanine Green (ICG) (shown in *Figure 4*) is the only approved organic dye for medical diagnostics and has been FDA approved for over 50 years for direct administration, commonly used to track blood flow and clearance.^{8,9,22} However, ICG is severely limited in biological applications due to its low quantum yield of 1.2%, Stokes shift of ~5 nm and exceptionally low stability.²³

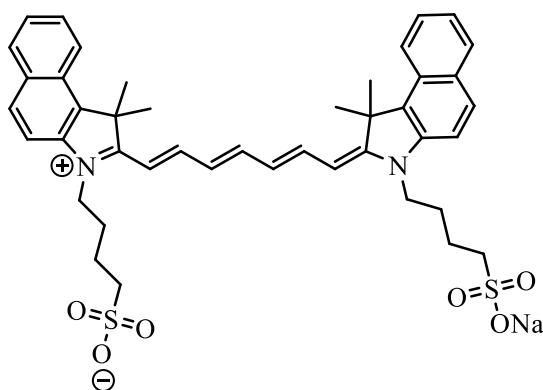


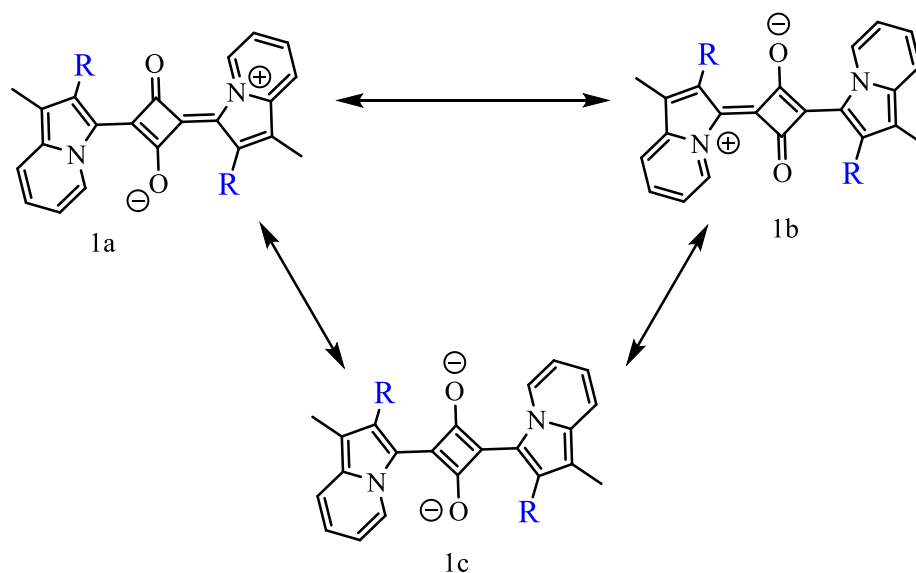
Figure 4. Molecular structure of Indocyanine Green.

Phthalocyanines and porphyrin derivatives consist of four bridged pyrrole subunits linked together through nitrogen atoms with a central cavity containing two hydrogen atoms. They are thermally and chemically very stable, and can support intense electromagnetic radiation.⁸ The central hydrogen atoms can be replaced with many metals, which allows for fine-tuning of the dyes spectral properties. However, most phthalocyanines and their derivatives still exhibit absorption and emission maxima below 700 nm, making their use for biological imaging very limited. Many phthalocyanines are studied for use in photodynamic therapy (PDT), as the dye is selectively taken up in

malignant and dysplastic tissues and irradiated, the central metal atom generates reactive singlet oxygen, which is cytotoxic to cells and can cause tumor death.^{8,12,22} However, applications are limited due to requiring high energy absorption and tuning to utilize lower energy light is synthetically challenging.

BODIPY (borondipyrrolemethene) dyes were originally discovered in 1968 by Triebs and Kreuzer.²⁴ They are thermally and chemically stable in physiological conditions, with high quantum yield and sharp fluorescence emissions. Few BODIPY dyes have emission maxima above 600 nm, making them again unsuitable for biological imaging applications.^{25,26} Research to tune absorption range is ongoing for with many research groups worldwide.

Squaraines consist of an oxycyclobutenolate core with aromatic or heterocyclic components at both ends of the molecule and exhibit a resonance-stabilized zwitterionic structure, shown in *Scheme 1*. Squaraines have extremely intense absorption bands, high molar absorptivity, good fluorescent quantum yield and strong fluorescence in solution.²⁷ However, they are typically planar and highly conjugated molecules resulting in hydrophobic structures, and few emit in the NIR region.⁸ Sulfonated derivatives with greatly increased water solubility and emission at about 800 nm have been reported by Umezawa et al., but the process of sulfonation reduced quantum yield to about 8% compared to non-sulfonated versions with a quantum yield of 44%.²⁸ Nakazumi et al. synthesized a series of bis-squaraines with pyrene or thiophene linkers and carboxyl end groups that exhibit emission maxima between 750-790 nm, with quantum yield again decreased to 0.01-1%.²⁹ We chose to target squaraines due to evidence for tunability with a focus on water solubility, Stokes shift and high quantum yield in the therapeutic window.



Scheme 1. Resonance-stabilization of indolizine-squaraine dyes.

Squaraines are the dicondensation product of two electron-rich aromatic or heterocyclic molecules (including N,N-dialkylanilines, benzothiazoles, phenols, azulenes and pyrroles) with squaric acid.³⁰ Substitution of the two donor units on zwitterionic squaraine dyes changes the intrinsic properties of the molecule and results in a variety of symmetric and unsymmetric squaraines with tunable optical properties. We have developed a series of twelve NIR emissive materials based on an indolizine donor and squaraine acceptor (bis(indolizine)-squaraine, or **In-SQ**), shown in *Figure 5*, which are of interest for a host of applications including living fluorescent biological imaging. For this application, the ideal material will (1) be water-soluble, (2) be stable in biological environments, (3) target the therapeutic window by both absorbing and emitting light between 650 and 900 nm, (4) have a relatively wide Stokes shift, (5) have strong adsorption and (6) have high fluorescence quantum yield. Squaraine derivatives have been proven to possess many of these characteristics, including intense absorption bands, high molar absorptivity coefficients, and good photoconductivity. However, because of their large,

planar, π -conjugated systems, many squaraine derivatives remain water insoluble, have poor Stokes shifts and have absorptions outside the therapeutic window. By using an indolizine donor moiety, these characteristics can be adjusted. By substituting an indolizine donor compared to the standard indoline donor, emission has been shown to red shift dramatically by ~ 100 nm, while the Stokes shift increases and water solubility improves. The shift in absorption wavelength can be justified by the generation of an proaromatic stabilized pyridinium during electron donation, as can be seen in *Scheme 1*.

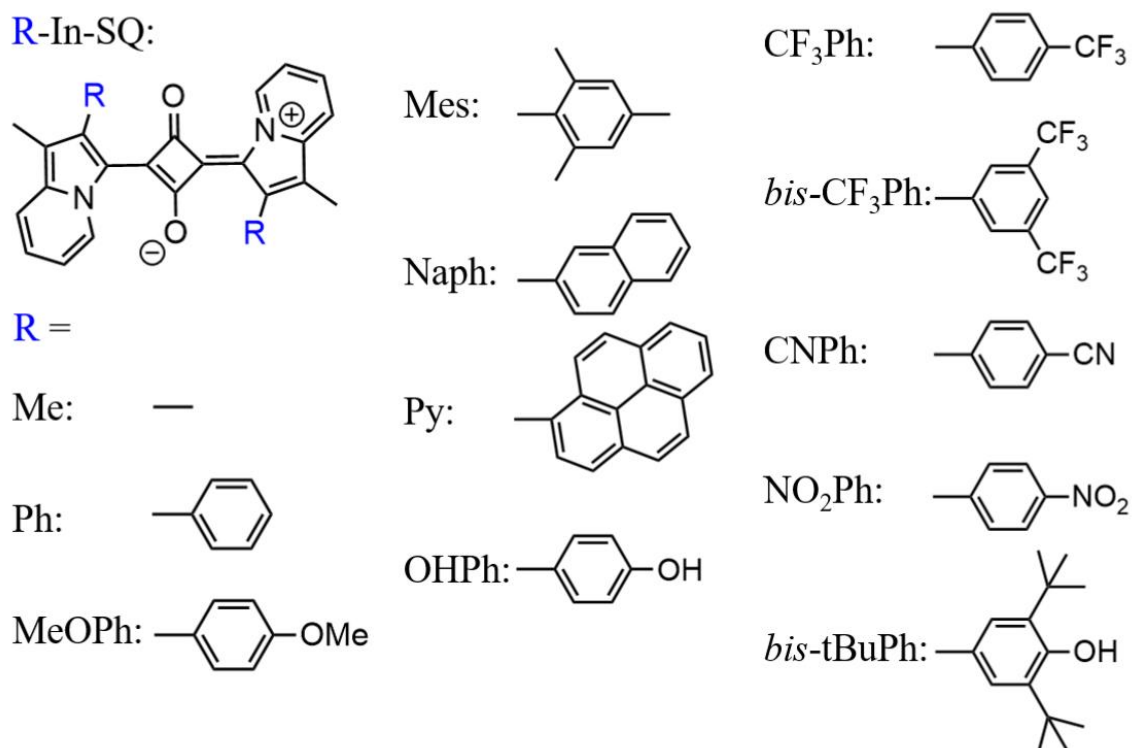


Figure 5. R-In-SQ series.

The benchmark bis(indoline)-squaraine (**ISQ**) molecule exhibits absorption and emission maxima at about 650 nm with a Stokes shift of 5 nm.³¹ Our series of dyes have a bis(indolizine)-squaraine (In-SQ) backbone, which is contrasted to **ISQ** in *Figure 6*.

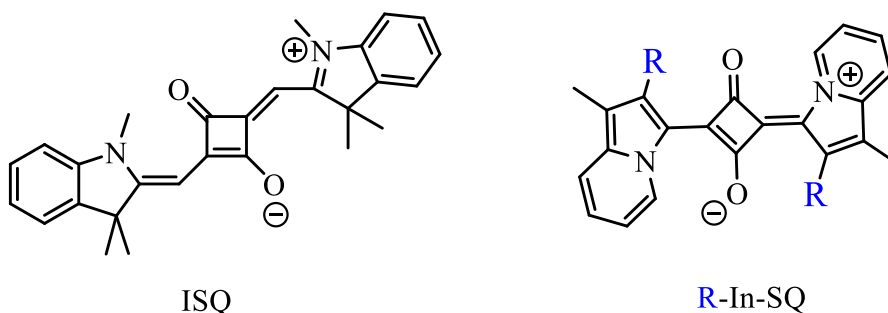


Figure 6. Comparison of **ISQ** and **R-In-SQ** dyes.

By making small modifications to the indolizine donor units, the absorption and emission maxima can be red shifted into the therapeutic window. The bathochromatic shift in absorption and emission spectra can be attributed to the increased electron density of the indolizine donor subunit and to an induced twist angle on the bis(indolizine)-squaraine molecular backbone compared to the completely flat, planar structure of **ISQ**, respectively. This twist be seen in *Figure 7*. The induced twist angle has also led to a lower hydrophobic shielding of the charged donor/squaraine core, which has led to an appreciable H₂O stability (fully miscible in a 1:1 H₂O: MeOH mixture).

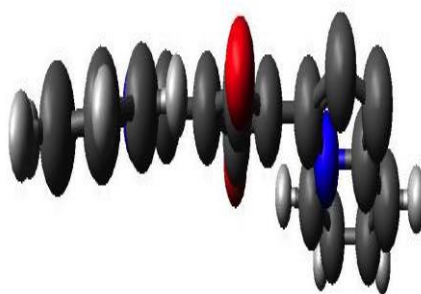


Figure 7. Computational study showing the twist angle of MeOPh-In-SQ.

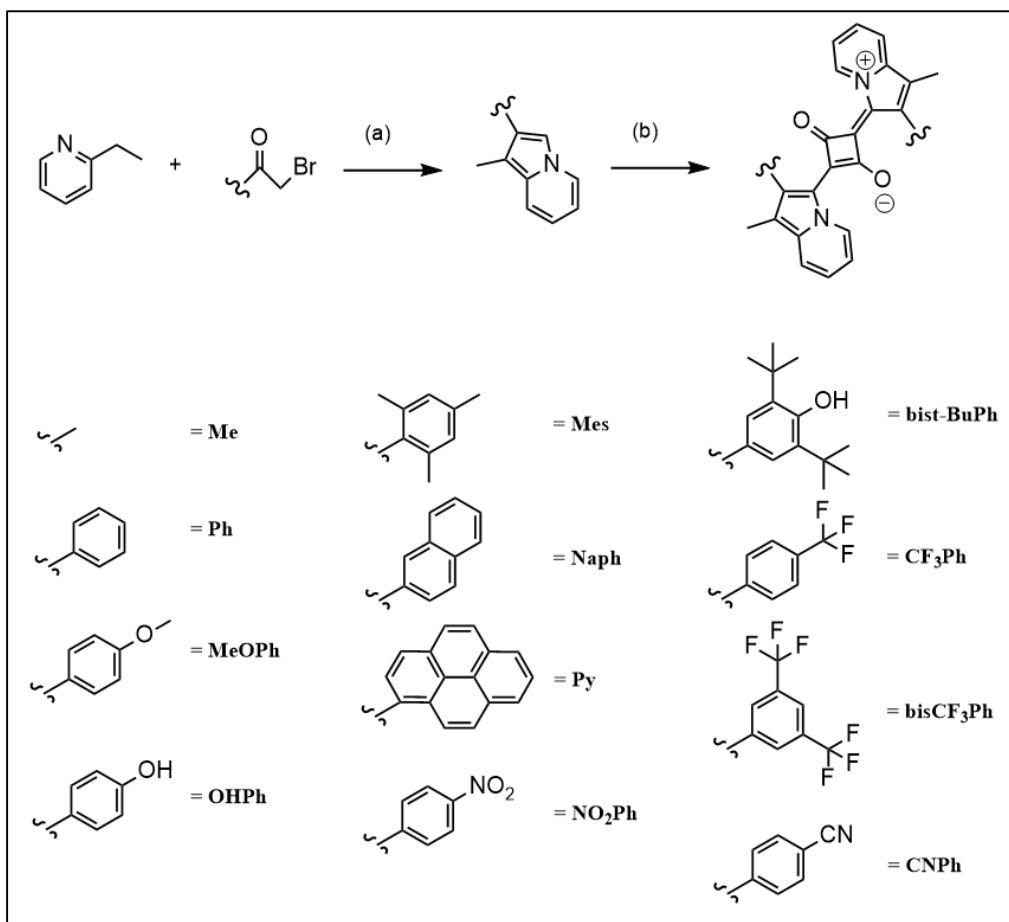
We hypothesize that this novel donor system will improve upon presently used donor moieties with wide-ranging applications. These molecules have demonstrated many

exciting characteristics, including water solubility resulting from sterically-induced molecular twist angles and long-wavelength absorption and emission characteristics that fall within the 650-900 nm range of the therapeutic window. Each of our materials has an absorption maxima (λ_{ABS}) of about 700 nm and emission maxima (λ_{EMS}) at about 750 nm, indicating a Stokes shift of about 50 nm. These attributes, compared to the standard indoline squaraine material, which has a Stokes shift of 12 nm and is completely planar (with poor solubility in water), are very promising for *in vivo* bioimaging.

Results and Discussion.

General Synthesis of R-In-SQ dyes:

The synthesis of the **R-In-SQ** series follows 2-synthetic steps according to *Scheme 2*. The indolizine ring is formed by a cyclization reaction with commercially available ethyl pyridine in a nucleophilic addition with a bromo-acetyl group in acetone, followed by condensation with sodium bicarbonate and water. The resulting electron-rich indolizine undergoes an electrophilic aromatic substitution with 0.5 equivalents of squaric acid to form the di-substituted squaraine dye. Purifications for all dyes were completed through recrystallization, without the use of silica gel chromatography.



Scheme 2. Synthetic scheme for **R-In-SQ** dye series. (a) i. ethyl-pyridine (1 equiv.), 0.5 M acetone, 60°C, 12-22 hr.; ii. sodium bicarbonate (4 equiv.), 1 M H₂O, 100°C, 2-7 hr.; 14%

(Me); 68% (Ph); 72% (MeOPh); 30% (Naph); 35% (OHPh); 92% (CF₃Ph); 54% (CNPh); 23% (NO₂Ph); 21% (bis-tBuPh); not isolated with high analytical purity (Mes, Py, bis-CF₃Ph);. (b) 3,4-dihydroxy-1,2-cyclobutanedione (0.5 equiv.), 0.035 M toluene, 0.035 M *n*-butanol, 130°C, 2.25-24 hr.; 61% (Me); 82% (Ph); 58% (MeOPh); 70% (Mes); 86% (Naph); 3% (Py); 95% (OHPh); 9% (CF₃Ph); 90% (bis-CF₃Ph); 25% (CNPh); 64% (NO₂Ph); 84% (bis-tBuPh).

Optical and Electrochemical Properties:

Making minor design changes to the **ISQ** structures yielded considerable effects on the optical and electrochemical dye parameters, summarized in *Table 1*. The induced twist angle produced by the indolizine donor caused a red shift in absorption and emission observed in all the molecules. In addition, the Stokes shift was observed to increase in all the molecules. Although the bis-2,4-substituted molecules exhibited high molar absorptivities (216,000 M⁻¹cm⁻¹, **bis-tBuPh-In-SQ**; 260,000 M⁻¹cm⁻¹, **bis-CF₃Ph-In-SQ**), they also demonstrated slightly smaller Stokes shifts (21 nm, **bis-tBuPh-In-SQ**; 33 nm, **bis-CF₃Ph-In-SQ**). No significant impact on quantum yield, λ_{max} or λ_{emis} was demonstrated due to presence of electron-donating or electron-withdrawing groups. However, extension of the π -ring as in **Py-In-SQ** and **Naph-In-SQ** resulted in lower molar absorptivity values (150,000 M⁻¹cm⁻¹ and 100,000 M⁻¹cm⁻¹, respectively) than for dyes without extensive conjugation without any significant red-shift in absorption or emission maxima or increase in Stokes shift. Highest quantum yields were observed in **Py-In-SQ**, **bis-tBuPh-In-SQ** and **bis-CF₃Ph-In-SQ** at 12.2%, 9.5% and 5.4%, respectively. Lowest quantum yield was observed in **Mes-In-SQ**, **OHPh-In-SQ** and **Ph-In-SQ** at 0.7%, 0.9%

and 2.1%, respectively. There was no strong correlation between electron donating or withdrawing groups and quantum yield, but the reduced quantum yield in **Mes-In-SQ**, **OHPH-In-SQ** and **Ph-In-SQ** may be due to reduced solubility in solution. Generally, as Stokes shift increased, quantum yields decreased with the one exception to this trend being **Py-In-SQ**, with a quantum yield of 12.2% and Stokes shift of 48 nm. Cyclic voltammetry measurements were made to analyze the influence of each indolizine donor on the electronic properties of the dyes. As can be seen in Table 2, the presence of electron-withdrawing groups on the donor subunit slightly increases the $E_{(S+/S)}$ and $E_{(S-/S)}$ values on the NHE scale (meaning these values are more stabilized energetically).

Table 2: UV-Vis-NIR absorbance and electrochemical data.

Dye (R-In-SQ)	λ_{\max} (nm)	λ_{onset} (nm)	λ_{emis} (nm)	Stokes shift (nm)	ϵ (M ⁻¹ cm ⁻¹)	E_g^{opt} (eV)	$E_{(S+/S)}$ [$E_{(S2+/S+)}$] (V)	$E_{(S-/S)}$ [$E_{(S2-/S-)}$] (V)	$E_{(S+/S^*)}$ (V)	Quantum Yield Φ
Me	706	738	760	52	210,000	1.68	1.32	-0.74	-0.36	-
Ph	716	753	778	62	181,000	1.65	1.40	-0.84	-0.25	0.0212
Mes	718 ^a	745 ^a	765 ^a	47	262,000	1.66	1.33	-0.84	-0.33	0.0074
Naph	720	756	776	56	150,000	1.64	1.30	-0.80	-0.34	0.0412
Py	722	752	770	48	100,000	1.65	1.26	-	-0.39	0.1224
MeOPh	716	750	776	60	140,000	1.65	1.27	-0.79	-0.38	0.0296
OHPH	716 ^c	755 ^c	774 ^c	58	185,000	1.64	-	-0.71	-0.38	0.0095
bis^tBuPh	716	738	737	21	216,000	1.68	1.30	-0.83	-0.38	0.0948
CF₃Ph	720	751	773	53	166,000	1.65	1.33	-0.71	-0.32	0.0247
bisCF₃Ph	720	746	753	33	260,000	1.66	1.44	-0.63	-0.22	0.0539
CNPh	723	753	777	54	213,000	1.65	1.31	-0.70	-0.34	0.0362
NO₂Ph	727	757	778	51	185,000	1.64	1.34 [0.85]	-0.64 [-0.93]	-0.30	0.0340
ISQ	659	-	671	12	229,000	-	1.17	-1.10	-	-

Solvent is Toluene. a- solvent is dichloromethane. b- irreversible reduction. c-solvent is 1:1 DCM:DMSO. UV/Vis spectra were measured with a Cary 5000 UV-Vis spectrometer with samples dissolved in dichloromethane. λ_{onset} values were taken at the intercept of a tangent line on the low energy side of the max absorption curve and the baseline. The optical bandgap (E_g^{opt}) was calculated according to the equation $E_g^{\text{opt}} = 1240/\lambda_{\text{onset}}$. $E_{(S+/S)}$ and $E_{(S-/S)}$ measurements were made in dichloromethane solution using a 0.1 M Bu₄NPF₆ electrolyte and ferrocene as an internal standard. All values are reported vs. NHE. $E_{(S+/S^*)}$ values were calculated according to the equation $E_{(S+/S^*)} = E_{(S+/S)} - E_g^{\text{opt}}$.

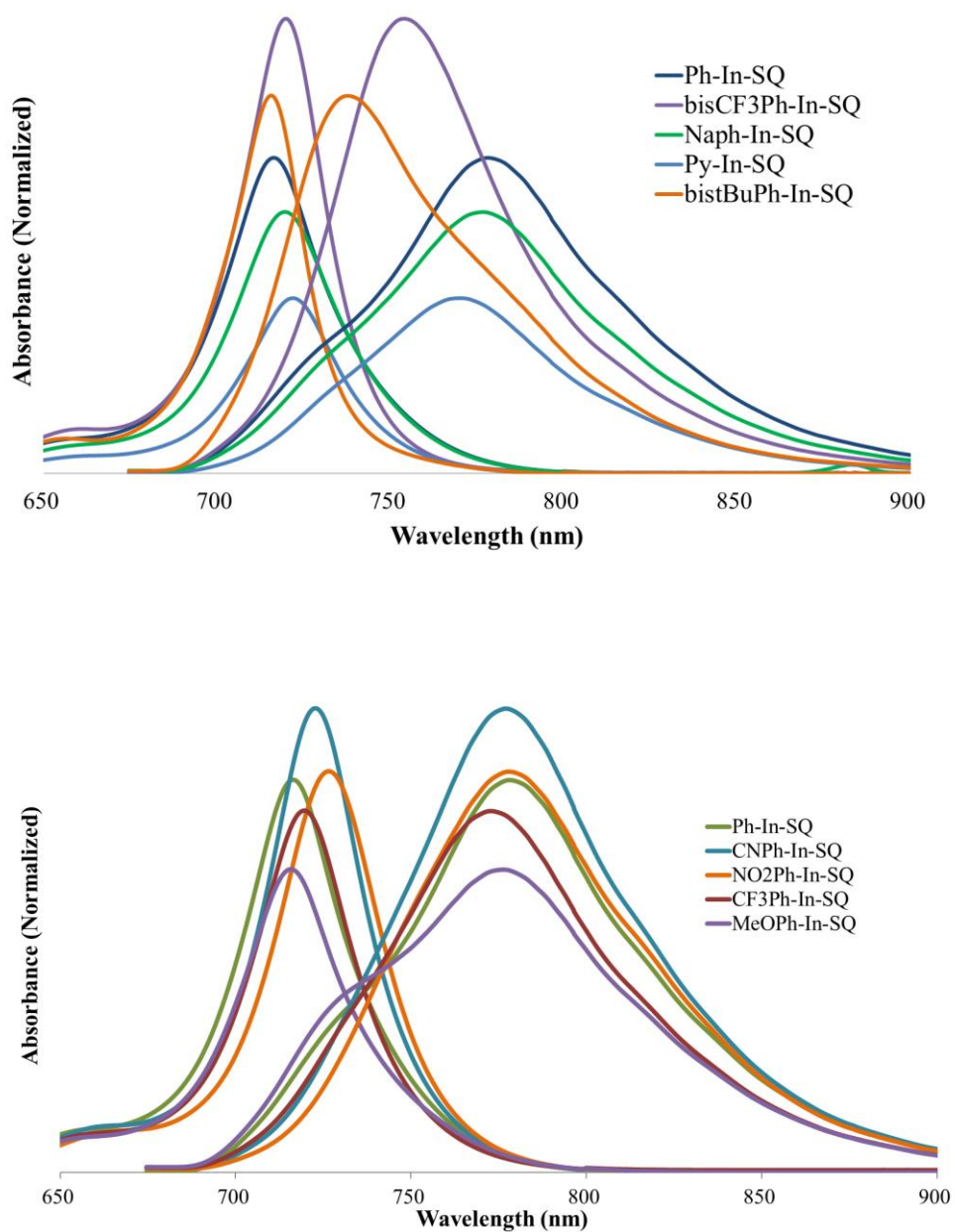


Figure 8. UV-vis absorption and emission spectra of **R-In-SQ** series dyes. All measurements were taken in dichloromethane solution.

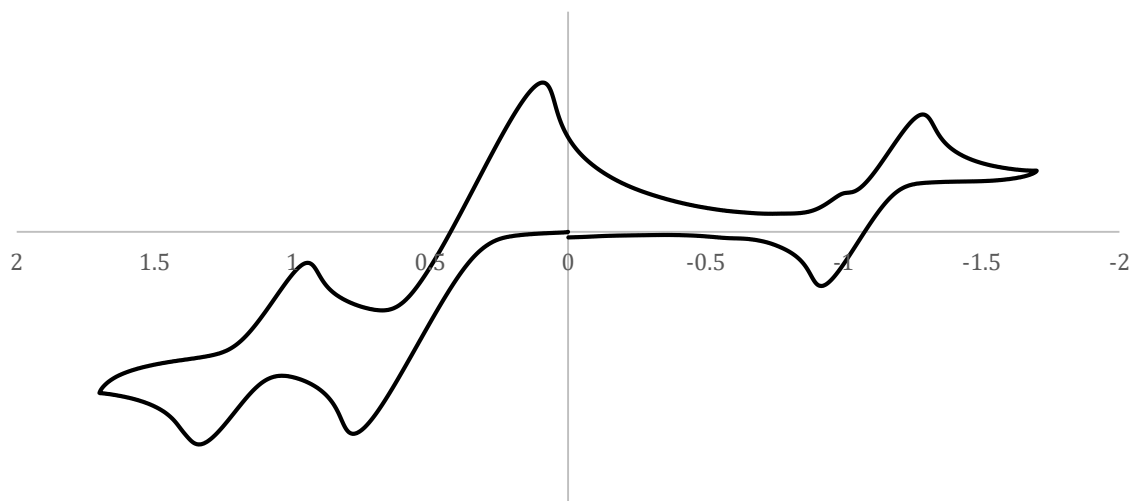


Figure 9. Cyclic voltammogram of **Ph-In-SQ**.

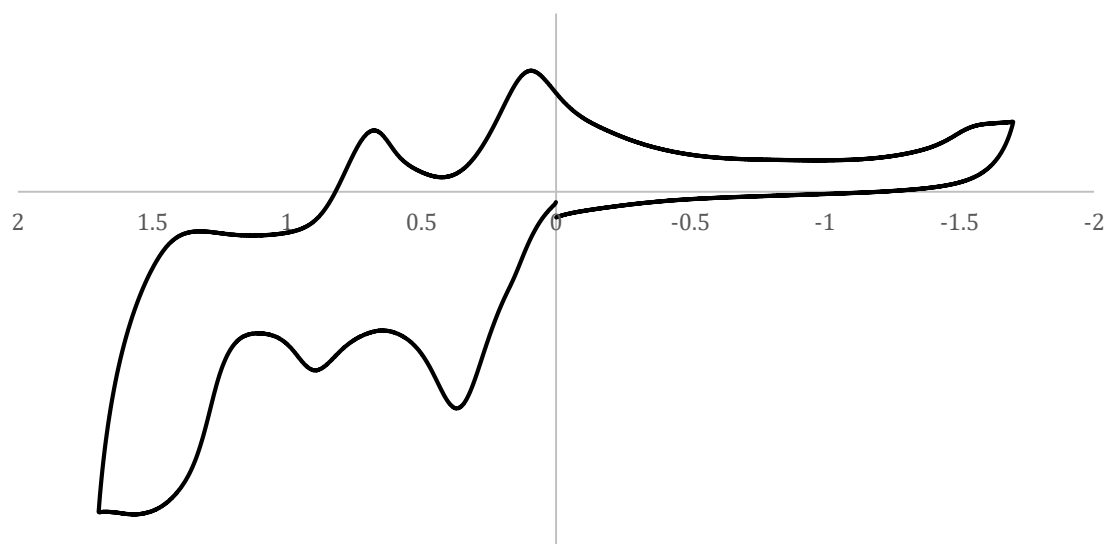


Figure 10. Cyclic voltammogram of **Py-In-SQ**.

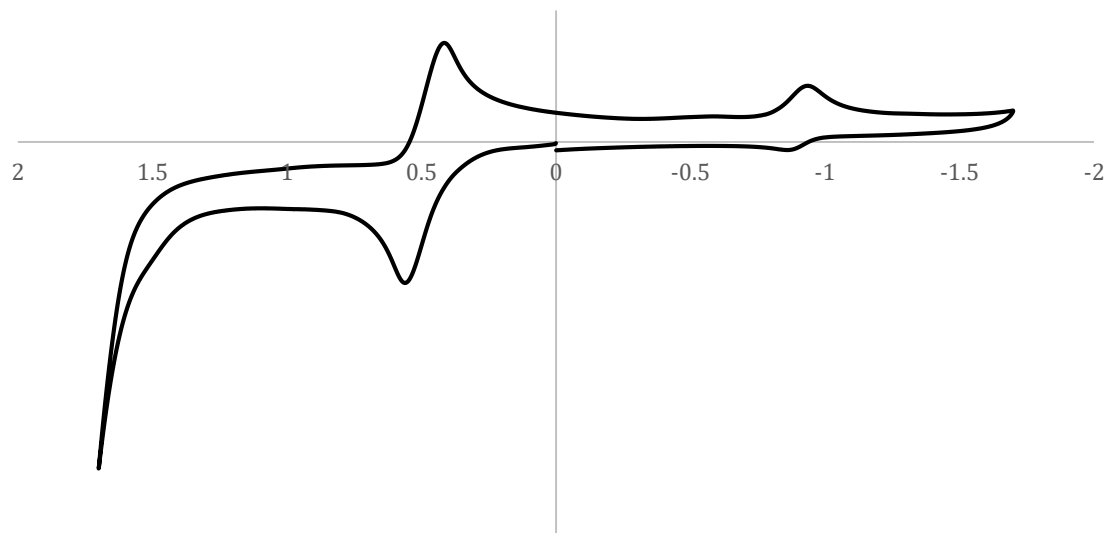


Figure 11. Cyclic voltammogram of **OHPH-In-SQ**.

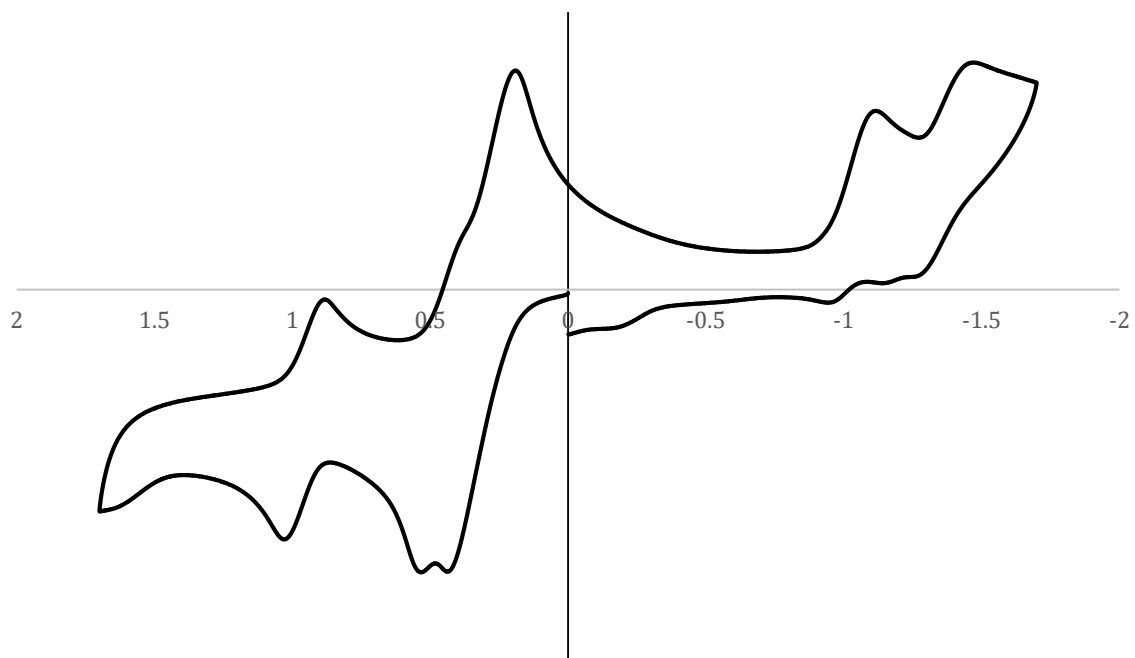


Figure 12. Cyclic voltammogram of **NO₂Ph-In-SQ**.

Conclusion.

We have successfully synthesized a series of indolizine-squaraine dyes intended for use in biological imaging. The **R-In-SQ** series of dyes were designed to incorporate an indolizine donor analogous of **ISQ**. All dyes in the **R-In-SQ** series exhibited a red shift in absorption and emission maximas well as an increased Stokes shift, as compared to **ISQ**. Through synthesis of twelve squaraines in this series, we were able to study substituent effects in addition to the change in donor from indoline to indolizine. A comparison of **Py-In-SQ** to **ISQ** shows a red shift in absorption maxima of ~60 nm (from 659 nm to 722 nm) and an increased Stokes shift of ~35 nm. This bathochromatic shift effectively translocates the absorption and emission of **Py-In-SQ** into the therapeutic window. The induced twist angle from substituting an indolizine donor moiety on **Py-In-SQ** allows appreciable water solubility through exposure of the charged squaraine core, compared to the insoluble **ISQ**. The molar absorptivity of **Py-In-SQ** has decreased by about 50% compared to **ISQ**, yet is still relatively high compared to other classes of organic emissive materials at 100,000 M⁻¹cm⁻¹. In addition, **Py-In-SQ** exhibited a quantum yield of 12% in solution, and squaraine dyes are inherently stable. Based on these displayed characteristics, the **R-In-SQ** series of dyes is promising for biological applications in particular and emissive materials in general. Future studies will include analyzing the substituent effects of additional water-solubilizing groups (such as sulfonated derivatives) to increase water solubility further.

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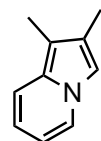
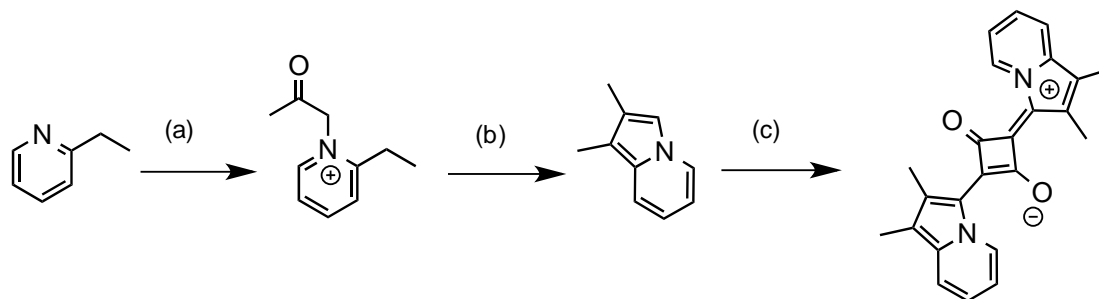
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Experimental Procedures.

General Information

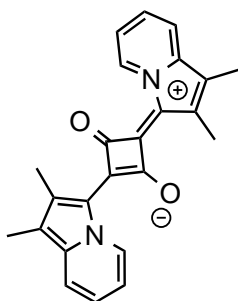
All commercially obtained reagents were used as received. Thin-layer chromatography (TLC) was conducted with Uniplat pre-coated Alumina GF or Sigma T-6145 pre-coated Silica gen 60 F₂₅₄ polyester sheets and visualized with UV. Flash column chromatography was performed as described by Still using Sorbent Tech P60, 40-63 μm (230-400 mesh). ¹H NMR spectra were recorded on a Bruker Avance-300 (300MHz) spectrometer and a Bruker Avance-500 (500MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data reported as s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad, ap = apparent, dd = doublet of doublets, dt = doublet of triplets; coupling constant(s) in Hz; integration. UV-Vis Spectra were measured with a Cary 5000 UV-Vis Spectrometer with samples dissolved in dichloromethane unless otherwise noted. Cyclic voltammetry was measured with a C-H Instruments electrochemical analyzer.

Synthetic Procedures: Me-In-SQ



1,2-dimethylindolizine (1): In a nitrogen filled round bottom flask equipped with a stir bar and a reflux condenser 2-ethylpyridine (2.00 g, 18.7 mmol) was mixed with chloroacetone (1.72 g, 18.7 mmol). The mixture was degassed with N₂ for 20 minutes,

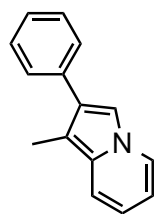
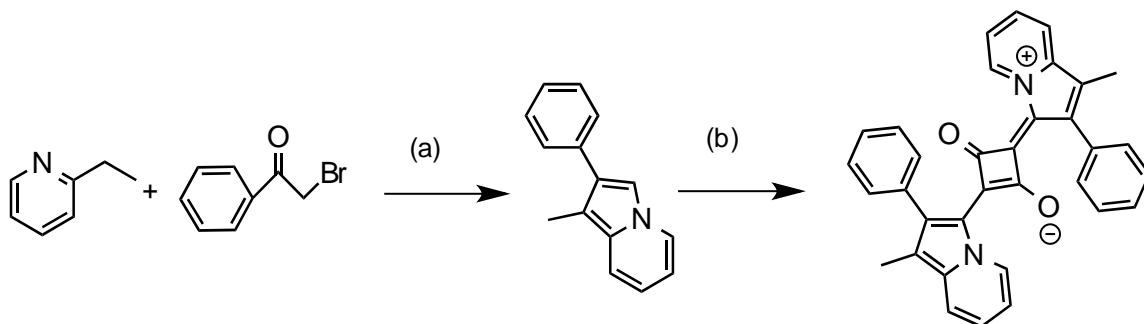
then heated to 130°C for 24 hours. The product was extracted with excess ethyl acetate and 2 M KOH and dried with sodium sulfate. The product was purified through aluminum oxide chromatography with 500 mL hexanes to yield the pure product (0.386 g, 14%). ¹H NMR (300MHz, CDCl₃) δ 7.76 (d, *J* = 10.0 Hz, 1 H), δ 7.235 (d, *J* = 5.0 Hz, 1 H), δ 7.10 (s, 1 H), δ 6.545 (t, *J* = 7.5 Hz, 1 H), δ 6.325 (t, *J* = 7.5 Hz, 1 H), δ 2.26 (s, 6 H).



(Z)-4-(1,2-dimethyl-3H-indolizin-4-ium-3-ylidene)-2-(1,2-dimethylindolizin-3-yl)-3-oxocyclobut-1-en-1-olate (2): In a flame dried round bottom flask equipped with a stir bar and reflux condenser, **(1)** (0.34 g, 2.34 mmol) was added with 3,4-dihydroxy-1,2-cyclobutanedione (0.12 g, 1.05 mmol), and degassed under N₂ for

10 minutes. The mixture was dissolved in 0.035 M dry, degassed toluene and 0.035 M dry n-butanol and refluxed for 20 hours. The reaction mixture was cooled to room temperature, and 500 mL diethyl ether was added to crash out a green solid. The liquid was decanted to yield the pure product (0.24 g, 61%). ¹H NMR (300 MHz, CDCl₃) δ 10.36 (d, *J* = 6.78 Hz, 2 H), δ 7.28 (2 H), δ 7.15 (t, *J* = 7.05 Hz, 2 H), δ 6.85 (t, *J* = 6.37 Hz, 2 H), δ 2.81 (s, 6 H), δ 2.21 (s, 6 H). ¹³C NMR (300 MHz, CDCl₃) unable to collect, product will not readily dissolve into an appropriate solvent. IR (neat, cm⁻¹): 3392.1 (br), 1625.7, 1623.7. UV-vis (CH₂Cl₂) λ_{max} = 706 nm (ε = 77,825 M⁻¹cm⁻¹), λ_{onset} = 740 nm.

Synthetic Procedures: Ph-In-SQ



1-methyl-2-phenylindolizine (4): To a round bottom flask equipped with a

stir bar and a reflux condenser was added 2-ethylpyridine (2.0 g, 18.7 mmol),

2-bromo-1-phenylethanone (3.72 g, 18.7 mmol) and 56.6 mL acetone. The

reaction mixture was heated to 60°C and stirred. After 20 hours, the reaction mixture was

cooled to room temperature and a white precipitate formed. The precipitate was filtered

and washed with 5 mL cold acetone, then transferred to a round bottom flask equipped

with a stir bar and reflux condenser and dissolved in 100 mL water with sodium bicarbonate

(6.72g, 75 mmol). The solution was heated to 100°C and allowed to stir. After 7 hours, the

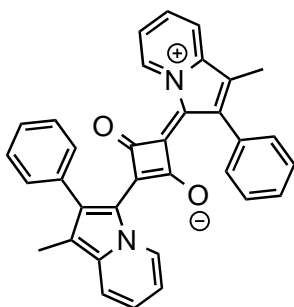
reaction mixture was cooled to room temperature and dark oil crystallized on top of the

water layer. The oil crystals were filtered and allowed to dry to yield the pure product (2.64

g, 68%). ¹H NMR (500 MHz, CDCl₃) δ 7.85 (dt, *J* = 7.0 Hz, 0.9 Hz, 1 H), δ 7.54 (d, *J* =

7.7 Hz, 1 H), δ 7.45 (7, *J* = 7.4 Hz, 1 H), δ 7.39 (s, 1 H), δ 7.35-7.29 (m, 2 H), δ 6.61 (ddd,

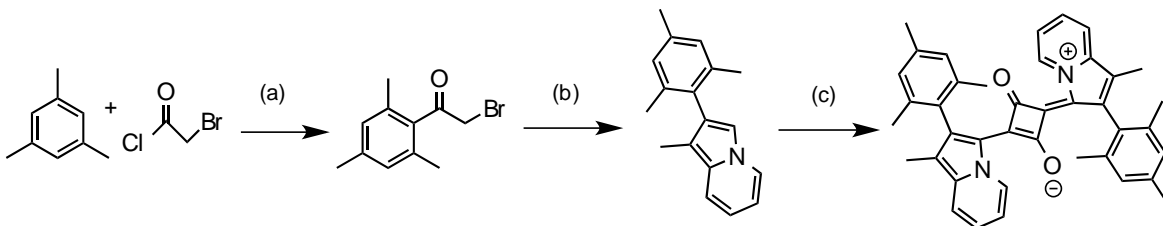
J = 7.1 Hz, 6.4 Hz, 1.0 Hz, 1 H), δ 6.42 (t, *J* = 6.8 Hz, 1 H), δ 2.45 (s, 3 H).

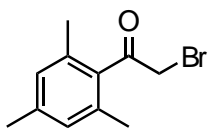


(Z)-4-(1-methyl-2-phenyl-3H-indolizin-4-ium-3-ylidene)-2-(1-methyl-2-phenylindolizin-3-yl)-3-oxocyclobut-1-en-1-olate

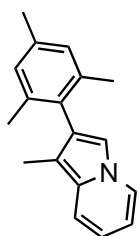
(5): To a flame dried round bottom flask equipped with a stir bar and reflux condenser was added **(4)** (0.50 g, 2.4 mmol), and 3,4-dihydroxy-1,2-cyclobutanedione (0.137 g, 1.20 mmol) then degassed under N₂ for 10 minutes. The mixture was dissolved in 136 mL 1:1 toluene:n-butanol then heated to 130°C for 15 hours. The mixture was cooled to room temperature, extracted with dichloromethane and washed three times with water. The product was purified through alumina chromatography with a gradient of 75:25 dichloromethane:hexanes then 98:2 dichloromethane:methanol and recrystallized in acetone and dichloromethane to yield a green solid (0.49 g, 82%). ¹H NMR (500 MHz, CDCl₃) δ 10.069 (d, J = 6.90 Hz, 2 H), δ 7.49-7.43 (m, 6 H), δ 7.39-7.35 (m, 6 H), δ 7.21 (t, J = 5.00 Hz, 2 H), δ 6.875 (t, J = 7.50, 2 H), δ 2.175 (s, 6 H). ¹³C NMR (300MHz, CDCl₃) δ 175.6, 168.5, 141.4, 137.5, 134.9, 134.7, 130.5, 127.6, 127.5, 126.8, 120.6, 118.2, 117.0, 114.9, 77.6, 77.2, 76.8, 9.5. IR (neat, cm⁻¹): 3401.7 (br), 2356.5, 2329.5, 2038.3, 1633.4, 1616.0. HRMS *m/z* calculated for C₃₄H₂₄N₂O₂ [M+H]⁺: 493.1916, found 493.1962. UV-vis (CH₂Cl₂) λ_{max} = 716 nm (ε = 180,618 M⁻¹cm⁻¹), λ_{onset} = 753 nm.

Synthetic Procedures: Mes-In-SQ





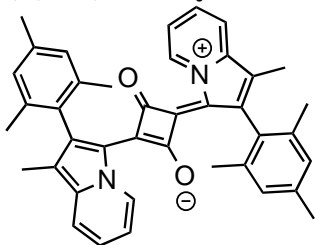
2-bromo-1-mesitylethanone (6): In a round bottom flask equipped with a stir bar, mesitylene (10 mL, 96.4 mmol) was added and cooled to 0°C. After 10 minutes, aluminum trichloride (1.7 g, 13 mmol) was added and allowed to cool for 5 minutes. 2-bromoacetyl chloride was added drop wise (6.00 mL, 72.0 mmol). The solution turned from yellow to orange, and was stirred while warming to room temperature for 15 hours. The reaction mixture was then poured into 100 mL cold H₂O and extracted twice with 150 mL Et₂O. The organic layer was washed with 50 mL saturated sodium bicarbonate, dried with magnesium sulfate, filtered and concentrated to yield the pure product (16.4 g, 94%). ¹H NMR (300 MHz, CDCl₃) δ 6.90 (s, 2H), δ 4.29 (s, 1 H), δ 2.32 (s, 3 H), δ 2.26 (s, 6H).



2-mesityl-1-methylindolizine (7): To a round bottom flask equipped with a stir bar and a reflux condenser was added (6) (2.41 g, 10 mmol) and 2-ethyl pyridine (1.14 mL, 10 mmol) and dissolved in 0.5 M acetone (20 mL). The mixture was heated to 60°C for 21 hours, in which no product was observed. The reaction mixture was then concentrated, dissolved in 20 mL acetone and heated to 150°C for 24 hours, then cooled to room temperature and poured into a 100 mL round bottom flask, dissolved in 70 mL H₂O and sodium bicarbonate (3.5 g, 40 mmol). The mixture was heated to 100°C for 2 hours, then cooled to room temperature, extracted with dichloromethane and concentrated. The product was passed through 200 mL SiO₂ using 30:70 hexanes:dichloromethane and concentrated to yield a mixture of (6) and (7), which was carried through to the next step. ¹H NMR (300 MHz, CDCl₃) δ 8.535 (d, J = 5.0 Hz, 1 H), δ 7.615 (t, J = 7.5 Hz, 1 H), δ 7.18 (d, J = 10.0 Hz, 1 H), δ 7.615 (t, J = 7.5 Hz, 1 H),

δ 7.115 (d, J = 7.5 Hz, 1 H), δ 6.88 (s, 2 H), δ 6.81 (s, 1 H), δ 2.31 (s, 3 H), δ 2.24 (s, 6 H), δ 2.29 (s, 3 H).

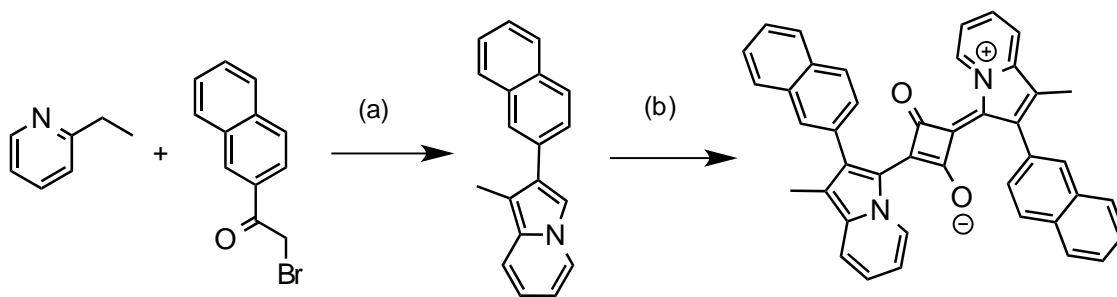
(Z)-4-(2-mesityl-1-methyl-3H-indolizin-4-ium-3-ylidene)-2-(2-mesityl-1-



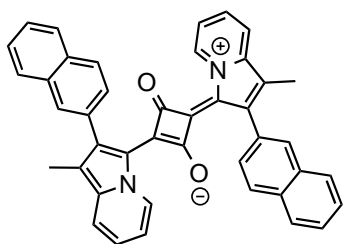
methylinolizin-3-yl)-3-oxocyclobut-1-en-1-olate) (8): To a

flame dried, round bottom flask equipped with a stir bar and a reflux condenser under N_2 , **(7)** (0.10 g, 0.40 mmol) was dissolved in 4 mL 1:1 toluene:n-butanol. 3,4-dihydroxy-1,2-cyclobutanedione (0.021 g, 0.18 mmol) was added and the mixture was heated to reflux for 1.5 hours, cooled to room temperature and concentrated to yield a red solid. The solid was suspended in diethyl ether, centrifuged, and the supernatant was decanted. The resulting solid was washed with hexanes (10 mL, 3 times) and dried to yield a bronze/red metallic solid (0.08 g, 70%). 1H NMR (300 MHz, $CDCl_3$) δ 10.1268 (d, J = 6.84 Hz, 2 H), δ 7.3103 (d, J = 8.70 Hz, 2 H), δ 7.1476 (t, J = 6.871 Hz, 2 H), δ 6.9335 (s, 4 H), δ 6.8335 (t, J = 6.81 Hz, 2 H), δ 2.3829 (s, 6 H), δ 1.9717 (s, 12 H), δ 1.983 (s, 6 H). ^{13}C NMR will not readily dissolve into solution. IR (neat, cm^{-1}): 3411.3903 (br), 1635.3074, 1616.0232. HRMS m/z calculated for $C_{34}H_{24}N_2O_2$ $[M+H]^+$: 577.2855, found 577.3189. UV-vis (CH_2Cl_2) λ_{max} = 718 nm (ϵ = 261,581 $M^{-1}cm^{-1}$), λ_{onset} = 745 nm.

Synthetic Procedures: Naph-In-SQ



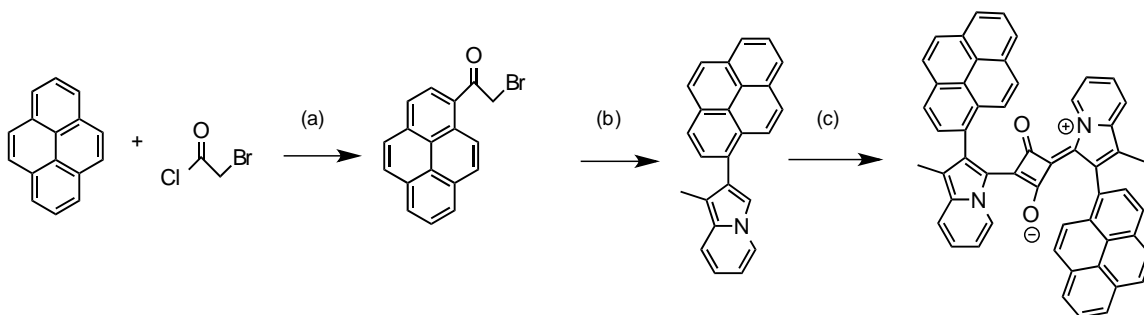
1-methyl-2-(naphthalene-2-yl)indolizine (9): To a flame dried, N₂ filled round bottom flask equipped with a stir bar and a reflux condenser was added 2-ethyl pyridine (0.215 g, 2.01 mmol), 2-bromo-2-(naphthalene-2-yl)ethan-1-one (0.5 g, 2.01 mmol) and 8 mL acetone. The solution was heated to 60°C and stirred. After 16 hours, a white precipitate had formed and the solution was cooled to room temperature. The precipitate was filtered and washed with cold acetone, then combined with sodium bicarbonate (0.086 g, 8.04 mmol) and dissolved in 32 mL water. The mixture was heated to 100°C under reflux. After 2 hours, a brown solid had formed. The solid was extracted with dichloromethane, washed three times with water, dried and concentrated to yield the pure product (0.153 g, 30%). ¹H NMR (300 MHz, CDCl₃) δ 7.96 (s, 1 H), δ 7.82-7.91 (m, 4 H), δ 7.68 (d, J = 8.25 Hz, 1 H), δ 7.42-7.53 (m, 3 H), δ 7.35 (d, J = 8.91, 1 H), δ 6.63 (t, J = 6.09 Hz, 1 H), δ 6.44 (t, J = 6.60 Hz, 1 H), δ 2.51 (s, 3 H). ¹³C NMR (300 MHz, CDCl₃) δ 133.7, 133.5, 132.1, 131.1, 129.0, 127.9 (2 C), 127.7, 127.4, 126.9, 126.1, 125.5, 124.8, 117.6, 115.8, 110.2, 110.1, 105.8, 9.8. IR (neat, cm⁻¹): 3050, 2965, 2919, 2860, 1626, 1598.

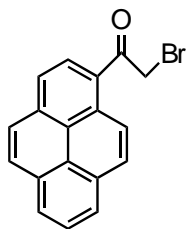


(Z)-4-(1-methyl-2-(naphthalen-2-yl)-3H-indolizin-4-ium-3-ylidene)-2-(1-methyl-2-(naphthalene-2-yl)indolizin-3-yl)-3-oxocyclobut-1-en-1-olate (10): To a

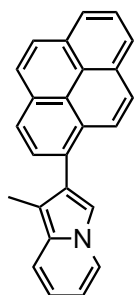
round bottom flask equipped with a stir bar and reflux condenser was added **(9)** (0.103 g, 0.401 mmol) and 3,4-dihydroxy-1,2-cyclobutanedione (0.013 g, 0.18 mmol), and flushed with N₂ for 10 minutes. The solids were then dissolved in 23 mL 1:1 toluene:n-butanol, and heated to 130°C for 2.25 hours during which a red precipitate formed. The mixture was cooled to room temperature, 50 mL diethyl ether was added and the liquid was decanted from the precipitate. To purify, the solids were dissolved in dichloromethane and recrystallized three times, then suspended in diethyl ether and centrifuged to yield a metallic red solid (0.102 g, 86%). ¹H NMR (300 MHz, CDCl₃) δ 7.77-7.90 (m, 2 H), δ 7.63-7.77 (m, 2 H), δ 7.40-7.56 (m, 3 H), δ 7.36 (d, J = 7.9 Hz, 1 H), δ 7.17 (t, J = 7.7 Hz, 1 H), δ 6.79 (t, J = 6.42 Hz, 1 H). ¹³C NMR will not dissolve into solution. IR (neat, cm⁻¹): 1600-3350 (br), 1594. UV-vis (CH₂Cl₂) λ_{max} = 720 nm (ε = 149,649 M⁻¹cm⁻¹), λ_{onset} = 756 nm.

Synthetic Procedures: Py-In-SQ

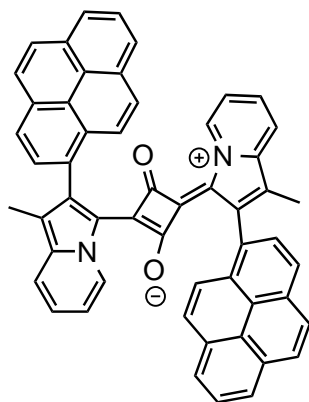




2-bromo-1-(pyren-4-yl)ethanone (11): In a flame dried round bottom flask equipped with a stir bar under N₂, aluminum trichloride (0.34 g, 2.97 mmol) was suspended in 2 mL dichloromethane and cooled to 0°C. 2-bromoacetyl chloride (0.215 mL, 2.60 mmol) was added slowly, then pyrene (0.50 g, 2.47 mmol) was added. The solution turned a deep red and was warmed to room temperature while stirring. After 3.5 hours, the mixture was diluted with 50 mL dichloromethane and washed with 25 mL H₂O. The organic layer was separated, then dried with magnesium sulfate, filtered and concentrated to yield the pure product (0.77 g, 96%). ¹H NMR (500 MHz, CDCl₃) δ 8.16 (d, *J* = 9.39 Hz, 1 H), δ 7.17-7.53 (m, 8 H), δ 4.71 (s, 2 H).



1-methyl-2-(pyren-2-yl)indolizine (12): In a round bottom flask equipped with a stir bar and a reflux condenser, **(11)** (0.75 g, 2.32 mmol) and 2-ethylpyridine (0.27 mL, 2.32 mmol) were dissolved in 10 mL acetone and heated to reflux. After 19 hours, the reaction mixture was cooled to room temperature and concentrated, then dissolved in 10 mL H₂O with sodium bicarbonate (0.78 g, 9.28 mmol) and heated to reflux for 3 hours. The solution was cooled to room temperature, then extracted with 100 mL dichloromethane, dried with magnesium sulfate, filtered and concentrated. ¹H NMR (500 MHz, CDCl₃) δ 8.38 (d, *J* = 10.0 Hz, 1 H), δ 7.87-8.23 (m, 9 H), δ 7.46 (s, 1 H), δ 7.44 (d, *J* = 5.0 Hz, 1 H), δ 6.71 (t, *J* = 5.0 Hz, 1 H), δ 6.48 (t, *J* = 7.5 Hz, 1 H), δ 2.31 (s, 3 H).

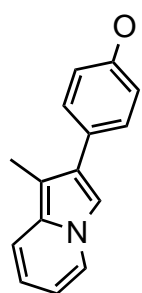
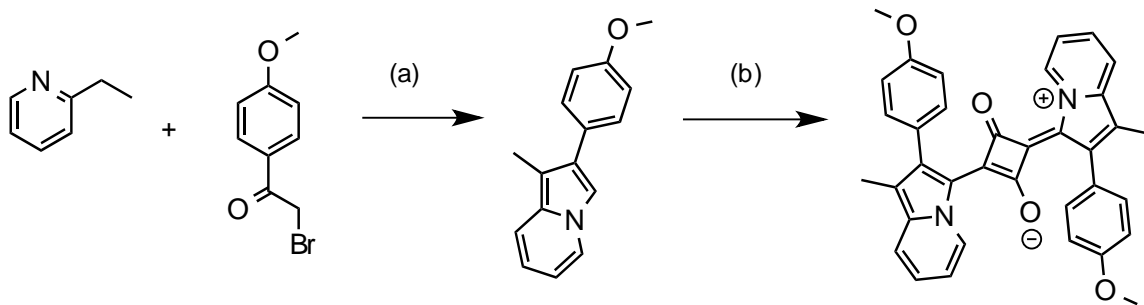


(Z)-4-(1-methyl-2-(pyren-2-yl)-3H-indolizin-4-ium-3-ylidene)-2-(1-methyl-2-pyren-2-yl)indolizin-3-yl)-oxocyclobut-1-en-1-olate (13):

To a flame dried round bottom flask equipped with a stir bar and dean-stark apparatus under N₂, (12) was added and dissolved in 10 mL 1:1 toluene:n-butanol, then heated to reflux. After 3 hours, the reaction mixture was

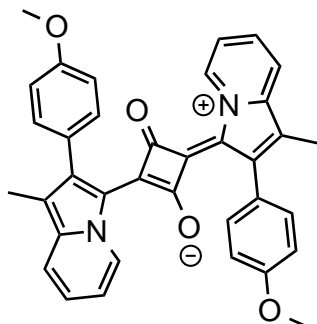
cooled to room temperature, the liquid was decanted from the mixture and a mixture of diethyl ether/hexanes was added to precipitate a green solid. The mixture was centrifuged and the resulting supernatant was decanted. To purify, 10 mL diethyl ether was added to the solid, centrifuged and decanted three more times, then the green solid was subjected to alumina oxide flash chromatography using 50% ethyl acetate / hexanes, concentrated, and dissolved in dichloromethane. Hexanes were added to the dichloromethane solution until a precipitate formed, then heated to reflux with a heat gun until the dichloromethane had evaporated. The solution was concentrated, and then dissolved in dichloromethane, precipitated by hexanes, refluxed and concentrated two more times to yield a blue/bronze metallic product (0.030 g, 3%). Rotomers present, ¹H NMR taken at variable temperature (T = 300 K, T = 345 K) to observe peak changes. ¹H NMR (300 MHz, CDCl₃) δ 9.967 (br s, 0.6 H), δ 9.549 (br s, 0.4 H), δ 8.3-7.8 (m, 6.2 H), δ 7.73 (d, J = 8.5 Hz, 0.7 H), δ 7.5-7.26 (m, 2.3 H), δ 7.25-7.0 (m, 1.8 H), δ 6.691 (br s, 0.6 H), δ 6.459 (br s, 0.4 H). ¹³C NMR rotomer issue. IR (neat, cm⁻¹): 2998.7066 (br), 1606.3811. HRMS *m/z* calculated for C₅₄H₃₂N₂O₂ [M+H]⁺: 741.2542, found 741.1421. UV-vis (CH₂Cl₂) λ_{max} = 722 nm (ε = 100,391 M⁻¹cm⁻¹), λ_{onset} = 752 nm.

Synthetic Procedures: MeOPh-In-SQ



2-(4-methoxyphenyl)-1-methylindolizine (14): To a round bottom flask equipped with a stir bar and reflux condenser, 2-ethylpyridine (4.99 mL, 43.64 mmol) and 2-bromo-1-(4-methoxyphenyl)ethanone (10.0 g, 43.64 mmol) were dissolved in 44 mL acetone and refluxed for 24 hours to yield a black precipitate. The precipitate was filtered, washed with cold acetone

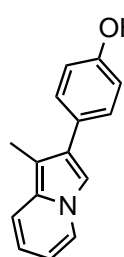
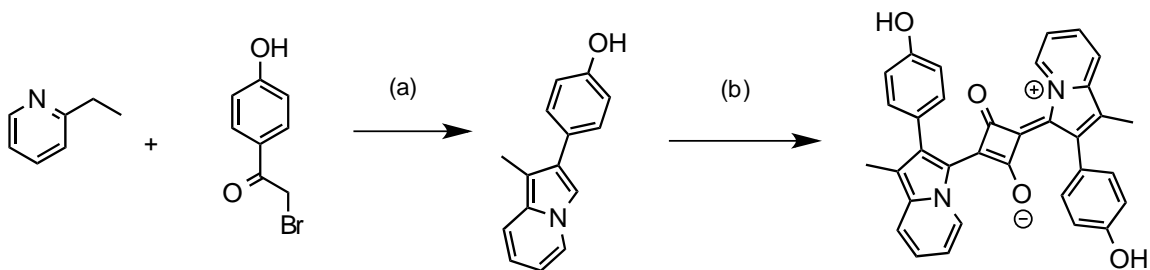
and allowed to dry. The solid was then added to a flask equipped with a stir bar and reflux condenser, dissolved in 88 mL H₂O with sodium bicarbonate (14.5 g, 174.6 mmol) and refluxed. After 2 hours, the mixture was cooled to room temperature to give a solid precipitate. The liquid was decanted, then the solid was dissolved in dichloromethane, dried with magnesium sulfate and filtered, subjected to SiO₂ chromatography with 4000 mL 1:1 ethyl acetate:dichloromethane and condensed to yield the pure product (7.44 g, 72%). ¹H NMR (300 MHz, CDCl₃) δ 7.8350 (d, *J* = 6.93 Hz, 1 H), δ 7.4474 (d, *J* = 6.69 Hz, 2 H), δ 7.3354 (s, 1 H), δ 7.3042 (d, *J* = 9.30 Hz, 1 H), δ 7.4762 (d, *J* = 8.79 Hz, 2 H), δ 6.5929 (t, *J* = 7.32 Hz, 1 H), δ 6.3935 (t, *J* = 6.63 Hz, 1 H), δ 3.8558 (s, 3 H), δ 2.4080 (s, 3 H).



(Z)-4-(2-(4-methoxyphenyl)-1-methyl-3H-indolizin-4-ium-3-ylidene)-2-(2-(4-methoxyphenyl)-1-methylindolizin-3-yl)-3-oxocyclobut-1-en-1-olate (15): To a flame dried round bottom flask equipped with a stir bar and dean stark apparatus under N₂ was added **(14)** (0.16 g, 0.69 mmol) and 3,4-

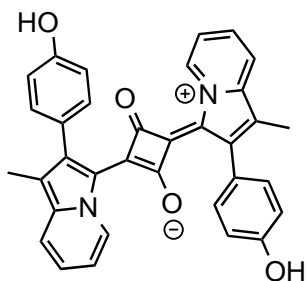
dihydroxy-1,2-cyclobutanedione (0.04 g, 0.35 mmol). The mixture was degassed with N₂ for 10 minutes, then dissolved in 20 mL 1:1 toluene:n-butanol and heated to 130°C with stirring. After 6 hours, the reaction mixture was condensed, dissolved in dichloromethane, washed with 50 mL H₂O three times, dried with magnesium sulfate and condensed to yield a metallic dark green solid (0.11 g, 58%). ¹H NMR (300 MHz, CDCl₃) δ 10.0991 (d, *J* = 6.78 Hz, 2 H), δ 7.3440 (d, *J* = 8.73 Hz, 2 H), δ 7.2501 (d, *J* = 5.94 Hz, 4 H), δ 7.1774 (t, *J* = 7.14 Hz, 2 H), δ 6.9676 (d, *J* = 8.61 Hz, 4 H), δ 6.8551 (t, *J* = 6.51 Hz, 2 H), δ 3.8664 (s, 6 H), δ 2.1881 (s, 6 H). ¹³C NMR (300 MHz, CDCl₃) δ 175.8547, 168.2807, 159.1101, 141.5192, 137.3907, 134.9318, 131.7630, 127.0735, 126.8220, 120.7107, 117.9745, 116.9169, 114.7445, 113.1887, 77.6565, 77.2335, 76.8099, 55.3494, 9.6079. IR (neat, cm⁻¹): 3395.9628 (br), 1633.3791 (s). HRMS *m/z* calculated for C₃₆H₂₈N₂O₄ [M+H]⁺: 553.2127, found 553.21. UV-vis (CH₂Cl₂) λ_{max} = 716 nm (ε = 139,513 M⁻¹cm⁻¹), λ_{onset} = 750 nm.

Synthetic Procedures: OHPH-In-SQ



4-(1-methylindolizin-2-yl)phenol (16): To a flame dried round bottom flask equipped with a stir bar and a reflux condenser was added 2-bromo-4'-hydroxyacetophenone (1.00 g, 4.65 mmol), 2-ethyl pyridine (0.498 g, 4.65 mmol) and dissolved in 18.6 mL acetone. The mixture was heated to 60°C

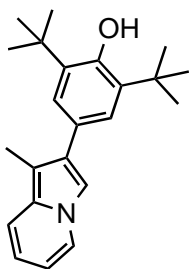
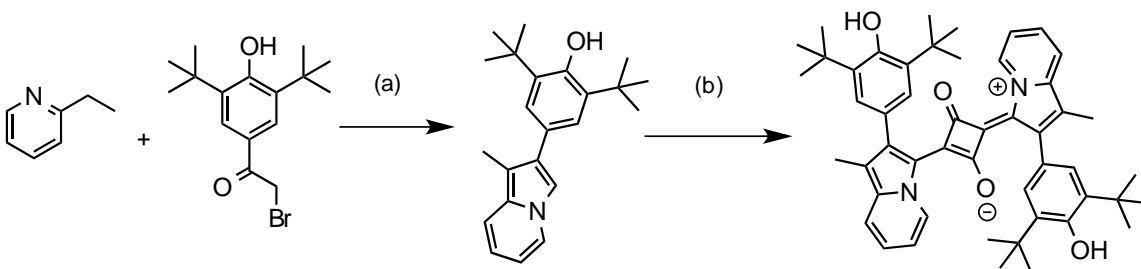
and stirred during which a fine white precipitate formed. After 18 hours, the mixture was cooled to room temperature and the precipitate was filtered off and washed with cold acetone. The precipitate was then added with sodium bicarbonate (1.56 g, 18.6 mmol) and 18.6 mL water to a round bottom flask, and the mixture was heated and stirred for 2 hours. After 2 hours, a dark brown oil had formed. The oil was extracted with dichloromethane, washed 3 time with 50 mL water, dried with sodium sulfate and condensed to yield an orange solid (0.356 g, 35%). ¹H NMR (300 MHz, CDCl₃) δ 7.76 (d, J = 6.96, 1 H), δ 7.33 (d, J = 8.46, 2 H), δ 7.21 (d, J = 9.87, 1 H), δ 6.84 (d, J = 8.49, 2 H), δ 6.53 (t, J = 7.72, 1 H), δ 6.32 (t, J = 6.66, 1 H), δ 4.8 – 5.1 (br s, 1 H), δ 2.34 (s, 3 H). ¹³C NMR (300 MHz, CDCl₃) δ 154.2, 130.9, 129.9, 128.72, 128.69, 124.7, 117.4, 115.6, 115.4, 109.9, 109.5, 105.4, 9.6. IR (neat, cm⁻¹): 3309.2, 1619.9, 1608.3.



(Z)-4-(2-(4-hydroxyphenyl)-1-methyl-3H-indolizin-4-ium-3-ylidene)-2-(2-(4-hydroxyphenyl)-1-methylindolizin-3-yl)-3-oxocyclobut-1-en-1-olate (17):

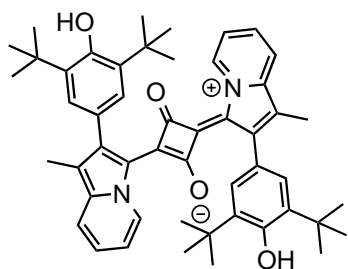
In a round bottom flask equipped with a stir bar and a reflux condenser was added **(16)** (0.326 g, 1.46 mmol), 3,4-dihydroxy-1,2-cyclobutanedione (0.075 g, 0.657 mmol) and dissolved in 80 mL 1:1 toluene:n-butanol. The mixture was heated to 130°C and stirred. After 6 hours, the reaction mixture was condensed, dissolved in dichloromethane, washed with 50 mL H₂O three times, dried with magnesium sulfate and condensed to yield the pure product. ¹H NMR (300 MHz, DMSO) δ 9.92 (d, J = , 2 H), δ 9.48 (s, 2 H), δ 7.72, (d, J = 9.15 Hz, 2 H), δ 7.43, (t, J = 7.20 Hz, 2 H), δ 7.14 (d, J = 8.58 Hz, 4 H), δ 7.11 (t, J = 6.46 Hz, 2 H), δ 6.82 (d, J = 8.55 Hz, 4 H), δ 2.21 (s, 6 H). ¹³C NMR (300 MHz, CDCl₃) δ will not dissolve into solution. IR (neat, cm⁻¹): 3397.89, 1641.09, 1639.16. UV-vis (CH₂Cl₂) λ_{max} = 716 nm (ε = 184,982 M⁻¹cm⁻¹), λ_{onset} = 755 nm.

Synthetic Procedures: bistBuPh-In-SQ



2,6-di-tert-butyl-4-(1-methylindolizin-2-yl)phenol (18): To a flame dried round bottom flask equipped with a stir bar and a reflux condenser was added 2-ethylpyridine (0.137 mL, 1.2 mmol), 2-bromo-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-ethanone (.393 g, 1.2 mmol) and 1.6 mL

acetone. The reaction mixture was heated to 65°C for 12 hours, then cooled to 0°C. The resulting precipitate was filtered and washed with cold acetone, then suspended in 2 mL H₂O. Sodium bicarbonate was added (0.403 g, 4.8 mmol), then the mixture was heated to 110°C for 2 hours. The mixture was cooled to room temperature, extracted with dichloromethane, washed 3 times with water and dried with sodium bicarbonate and concentrated to yield the pure product (.083 g, 21%). ¹H NMR (500 MHz, CDCl₃) δ 7.8381 (br s, 1 H), δ 7.25-7.40 (m, 4 H), δ 6.5817 (br s, 1 H), δ 6.3835 (br s, 1 H), δ 5.1815 (s, 1 H), δ 2.4220 (s, 3 H), δ 1.4921 (s, 18 H). ¹³C NMR (300 MHz, CDCl₃) δ 152.8, 136.0, 131.1, 130.2, 127.2, 125.7, 124.8, 117.5, 115.6, 109.9, 109.6, 105.5, 77.6, 77.2, 76.8, 34.6, 30.6, 9.9. IR (neat, cm⁻¹): 3627.37429 (s), 2942.424263, 2908.0704, 2863.8765. HRMS *m/z* calculated for C₂₃H₂₉NO [M+H]⁺: 336.2327, found 336.2327.

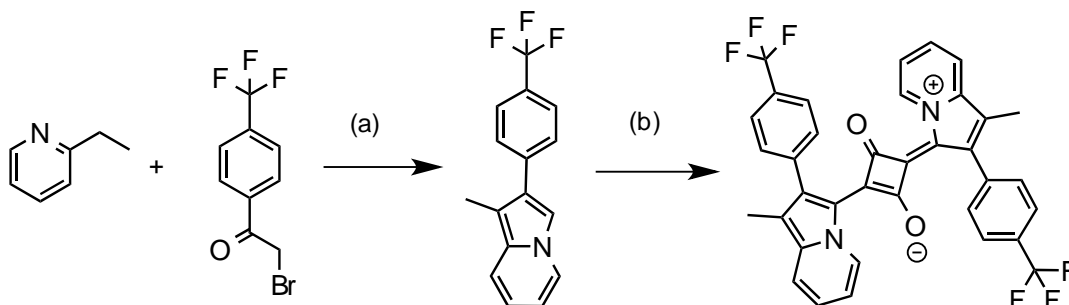


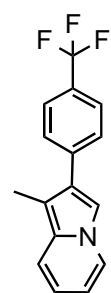
(Z)-4-(2-(3,5-di-tert-butyl-4-hydroxyphenyl)-1-methyl-3H-indolizin-4-ium-3-ylidene)-2-(2-(3,5-di-tert-butyl-4-hydroxyphenyl)-1-methylindolizin-3-yl-3-oxocyclobut-1-en-1-olate (19): To a flame dried round bottom flask

equipped with a stir bar and a reflux condenser was added **(18)** (69.0 mg, 0.206 mmol), 3,4-dihydroxy-1,2-cyclobutanedione (10.5 mg, 0.0925 mmol), n-butanol (5.88 mL), and toluene (5.88 mL). The reaction was heated to 130°C for 15 hours, then cooled to room temperature. The reaction was extracted with dichloromethane, washed three times with water and dried with magnesium sulfate. The product was purified through silica gel chromatography in dichloromethane, and then triturated in ethyl acetate to give a red solid. ¹H NMR (300 MHz, CDCl₃) δ 9.90 (d, *J* = 6.90 Hz, 1H), 7.37 (d, *J* = 8.61 Hz, 1H), 7.21

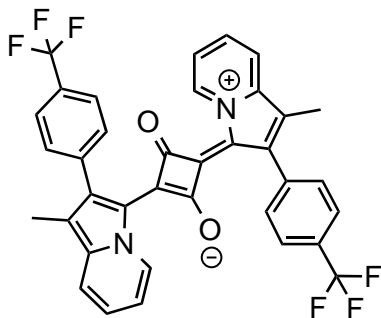
(s, 1H), 7.16 (d, $J = 8.73$, 1H), 6.77 (t, $J = 6.21$ Hz, 1H), 5.29 (d, $J = 3.36$ Hz, 1H), 2.32 (s, 3H) 1.48 (s, 18H). ^{13}C NMR not possible, will not dissolve into solution. IR (neat, cm^{-1}): 3419.1040 (br), 1652.6634. HRMS m/z calculated for $\text{C}_{50}\text{H}_{56}\text{N}_2\text{O}_4$ [M]: 748.4240, found 748.4153. UV-Vis (CHCl_3): $\lambda_{\text{max}} = 716$ nm ($\epsilon = 216,101 \text{ M}^{-1}\text{cm}^{-1}$), $\lambda_{\text{onset}} = 738$.

Synthetic Procedures: $\text{CF}_3\text{Ph-In-SQ}$



 **1-methyl-2-(4(trifluoromethyl)phenyl)indolizine (20):** To a flame dried, round bottom flask equipped with a stir bar and a reflux condenser, 2-ethyl pyridine (1.07 mL, 9.33 mmol) and 2-bromo-1-(4-(trifluoromethyl)-phenyl)ethanone (2.49 g, 9.33 mmol) were dissolved in 20 mL acetone and heated to reflux. After 22 hours, the reaction mixture was cooled to room temperature and concentrated. The resulting solid was dissolved in 20 mL H_2O and sodium bicarbonate (3.13 g, 37.3 mmol). The mixture was refluxed for 2 hours and cooled to room temperature during which dark crystals formed. The crystals were filtered and washed with cold water to yield the pure product (2.36 g, 92%). ^1H NMR (500 MHz, CDCl_3) δ 7.855 (d, $J = 6.00$ Hz, 1 H), δ 7.671 (d, $J = 8.00$ Hz, 2 H), δ 7.624 (d, $J = 8.0$ Hz, 2 H), δ 7.414 (s, 1 H), δ 7.339 (d, $J = 9.0$ Hz, 1 H), δ 6.639 (t, $J = 6.50$ Hz, 1 H), δ 6.447 (t, $J = 6.50$ Hz, 1 H). ^{13}C NMR (300 MHz, CDCl_3) δ 149.00, 139.88, 136.52, 131.27, 128.65, 127.53, 125.36, 124.81, 117.64, 116.15,

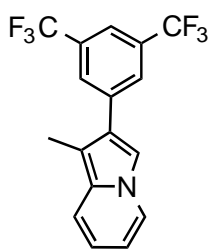
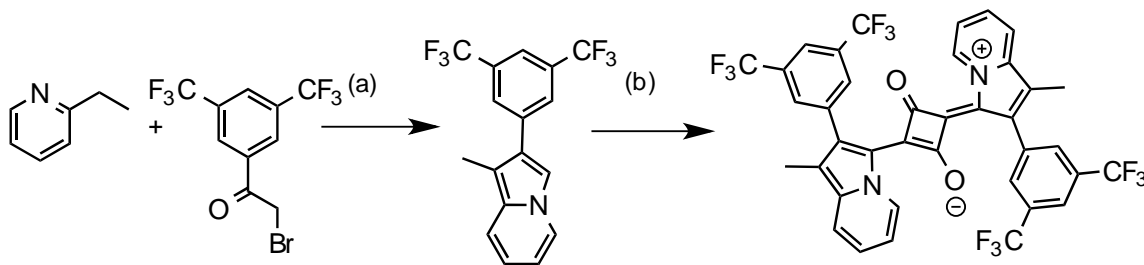
110.58, 110.13, 105.679.64. IR (neat, cm^{-1}): 3399.8197 (br), 3070.0584, 2919.6409, 1683.5182, 1616.1241. HRMS m/z calculated for $\text{C}_{16}\text{H}_{12}\text{F}_3\text{N}$ $[\text{M}+\text{H}]^+$: 276.1000, found 276.1318.



(Z)-4-(1-methyl-2-(4-(trifluoromethyl)phenyl)-3H-indolizin-4-ium-3-ylidene)-2-(1-methyl-2-(4-trifluoromethyl)phenyl)indolizin-3-yl)-3-oxocyclobut-1-en-1-olate (21): To a flame dried, round bottom flask equipped with a stir bar and condenser under N_2 , **(20)** (0.10

g, 0.36 mmol) and 3,4-dihydroxy-1,2-cyclobutanedione (0.021 g, 0.18 mmol) were dissolved in 4 mL 1:1 toluene:n-butanol and heated to reflux. After 24 hours, the reaction mixture was cooled to room temperature and a dark green precipitate formed. Diethyl ether was added and a metallic yellow/bronze precipitate was observed. The mixture was centrifuged and the resulting supernatant was decanted. To purify, diethyl ether was again added to the precipitate, centrifuged and the supernatant was decanted 2 additional times. Then, the precipitate was washed with hexanes to yield a metallic green solid (0.01 g, 9%). ^1H NMR (300 MHz, CDCl_3) δ 10.141 (d, $J = 6.90$, 2 H), δ 7.653 (d, $J = 8.40$ Hz, 4 H), δ 7.408 (d, $J = 8.10$ Hz, 4 H), δ 7.3935 (d, $J = 7.50$ Hz, 2 H), δ 7.241 (t, $J = 6.75$ Hz, 2 H), δ 6.924 (t, $J = 6.90$ Hz, 2 H), δ 2.163 (s, 6 H). ^{13}C NMR (300 MHz, CDCl_3) δ 141.540, 138.440, 136.093, 135.043, 130.905, 129.787, 129.385, 127.543, 122.928, 120.625, 118.953, 117.340, 115.595, 9.558. IR (neat, cm^{-1}): 3380.5354 (br), 1616.0232. HRMS m/z calculated for $\text{C}_{36}\text{H}_{22}\text{F}_6\text{N}_2\text{O}_2$ $[\text{M}]$: 628.1585, found 628.1810. UV-vis (CH_2Cl_2) $\lambda_{\text{max}} = 720$ nm ($\epsilon = 166,402 \text{ M}^{-1}\text{cm}^{-1}$), $\lambda_{\text{onset}} = 751$ nm.

Synthetic Procedures: *bis*CF₃Ph-In-SQ

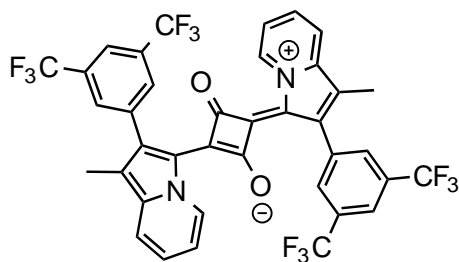


2-(3,5-bis(trifluoromethyl)phenyl)-1-methylindolizine (22): To a flame dried round bottom flask equipped with a stir bar and a reflux condenser was added 1-(3,5-bis(trifluoromethyl)phenyl)-2-bromoethan-1-one (0.8 g, 2.38 mmol), 2-ethyl pyrrole (0.255 g, 2.38

mmol) and 10 mL acetone. The mixture was heated to 60°C and stirred, during which a white precipitate formed. After 16 hours, the solution was cooled to room temperature, and the white precipitate was filtered off and washed with cold acetone. The precipitate was then combined with sodium bicarbonate (0.802 g, 9.55 mmol) in a round bottom flask and dissolved in 10 mL water. The solution was heated to 100°C and stirred for 2 hours. After 2 hours a brown oil had formed, and was extracted with dichloromethane. The organic layer was washed three times with water, dried and concentrated to yield the pure product.

¹H NMR (300 MHz, CDCl₃) δ 7.94 (s, 2 H), δ 7.87 (d, J = 6.9 Hz, 1 H), δ 7.79 (s, 1 H), δ 7.46 (s, 1 H), δ 7.35 (d, J = 9.03 Hz, 1 H), δ 6.67 (t, J = 6.7 Hz, 1 H), δ 6.48 (t, J = 6.7 Hz, 1 H), δ 2.43 (s, 3 H). ¹³C NMR (300 MHz, CDCl₃) δ 138.3, 131.9, 131.5, 131.4, 128.3, 126.1, 124.8, 117.7, 116.5, 110.9, 110.1, 105.6, 9.4.

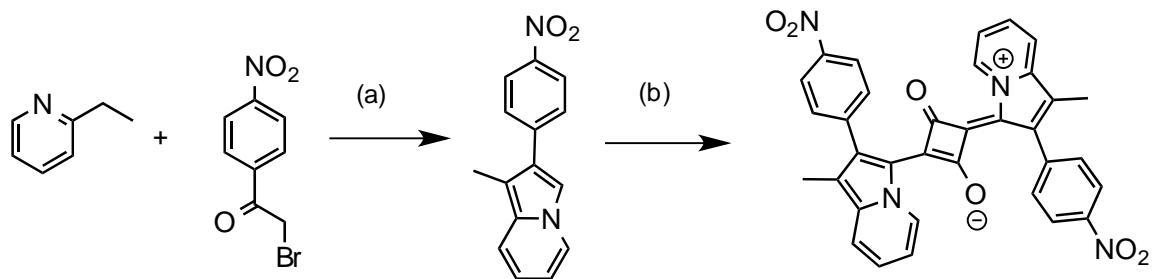
IR (neat, cm⁻¹): 3232 (br), 2923, 2866, 1617.

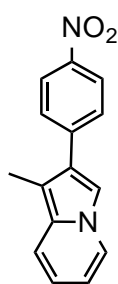


(Z)-4-(2-(3,5-bis(trifluoromethyl)phenyl)-1-methyl-3H-indolizin-4-ium-3-ylidene)-2-(2-(3,5-bis(trifluoromethyl)phenyl)-1-methylindolizin-3-yl)-3-oxocyclobut-1-en-1-olate (23): To a N₂ filled,

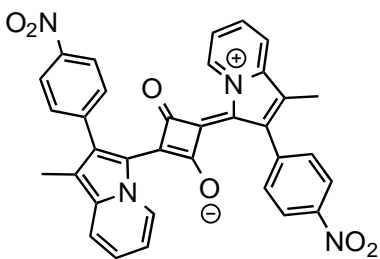
round bottom flask equipped with a stir bar and a reflux condenser was added **(22)** (0.235 g, 0.685 mmol), 3,4-dihydroxy-1,2-cyclobutanedione (0.0389 g, 0.342 mmol) and dissolved in 40 mL 1:1 toluene:n-butanol. The mixture was heated to 130°C and stirred. After 6 hours, the mixture was cooled to room temperature and 50 mL diethyl ether was added to precipitate a dark solid. The liquid was decanted and the solids were collected. To purify, the solids were dissolved in hot dichloroethane and filtered. The solution was cooled at room temperature, and dark solids precipitated at the bottom of the flask with a bright green solution. The solids were separated from the supernatant to yield the pure metallic product. ¹H NMR (300 MHz, CDCl₃) δ 9.99 (d, J = 6.3 Hz, 2 H), δ 7.90 (s, 2 H), δ 7.74 (s, 4 H), δ 7.45 (d, J = 8.61, 2 H), δ 7.30 (t, J = 7.59, 2 H), δ 6.98 (t, J = 6.72, 2 H), δ 2.23 (s, 6 H). ¹³C NMR (300 MHz, CDCl₃) will not dissolve into solution. IR (neat, cm⁻¹): 3415.25, 1573.58, 1556.24. UV-vis (CH₂Cl₂) λ_{max} = 720 nm (ε = 260,205 M⁻¹cm⁻¹), λ_{onset} = 746 nm.

Synthetic Procedures: NO₂Ph-In-SQ





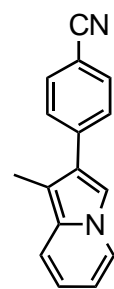
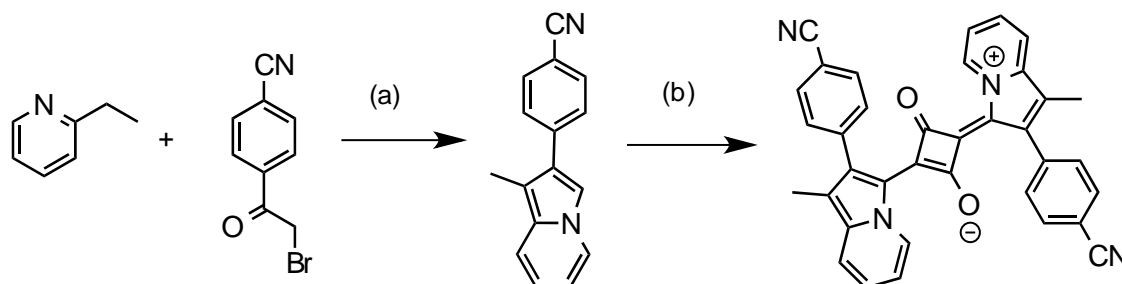
1-methyl-2-(4-nitrophenyl)indolizine (24): To a flame dried round bottom flask equipped with a stir bar and a reflux condenser was added 2-bromo-4'-nitroacetophenone (1.0 g, 4.10 mmol) and 2-ethyl pyridine (0.439 g, 4.10 mmol) and dissolved in 16.4 mL acetone. The mixture was heated to 60°C and stirred. After 16 hours, the solution was cooled to room temperature, and the white precipitate was filtered off and washed with cold acetone. The precipitate was then combined with sodium bicarbonate (1.38 g, 16.4 mmol) in a round bottom flask and dissolved in 16.4 mL water. The solution was heated to 100°C and stirred for 2 hours. After 2 hours brown oil had formed, and was extracted with dichloromethane. The organic layer was washed three times with water, dried with sodium sulfate and concentrated. To purify, the product was filtered through silica with 1:1 dichloromethane:hexanes and concentrated to yield a orange powder (0.237 g, 23%). ¹H NMR (300 MHz, CDCl₃) δ 8.27 (d, J = 8.7 Hz, 2 H), δ 7.86 (d, J = 6.8 Hz, 1 H), δ 7.67 (d, J = 8.7 Hz, 2 H), δ 7.46 (s, 1 H), δ 7.35, (d, J = 9.2 Hz, 1 H), δ 6.66 (t, J = 6.7 Hz, 1 H), δ 6.47 (t, J = 6.5 Hz, 1 H), δ 2.46 (s, 3 H). ¹³C NMR (300 MHz, CDCl₃) δ 146.1, 143.2, 131.5, 128.7, 126.6, 124.8, 123.9, 117.8, 116.5, 111.0, 110.4, 105.9, 9.8. IR (neat, cm⁻¹): 3361.25, 3108.63, 1594.81.



(Z)-4-(1-methyl-2-(4-nitrophenyl)-3H-indolizin-4-ium-3-ylidene)-2-(1-methyl-2-(4-nitrophenyl)indolizin-3-yl)-3-oxocyclobut-1-en-1-olate (25): To a N₂ filled round bottom flask equipped with a stir bar and a reflux condenser was added **(24)** (0.118 g, 0.468 mmol), 3,4-dihydroxy-1,2-cyclobutanedione

(0.027 g, 0.234 mmol) and dissolved in 13.4 mL toluene:n-butanol. The mixture was heated to 130°C and stirred. After 24 hours the mixture was cooled to room temperature and 50 mL 1:1 diethyl ether:hexanes was added. A red solid precipitated and the liquid was decanted off. The solids were recrystallized in dichloromethane and concentrated to yield a metallic red solid (0.088 g, 64%). ¹H NMR (300 MHz, CDCl₃) δ 10.13 (d, J = 5.22, 2 H), δ 8.28 (d, J = 8.58 Hz, 4 H), δ 7.46 (d, J = 8.85, 4 H), δ 7.43 (d, J = 9.93, 2 H), δ 7.23 (hidden by CDCl₃), δ 6.45 (t, J = 6.45 Hz, 2 H), 2.18 (s, 6 H). ¹³C NMR (300 MHz, CDCl₃) δ will not dissolve into solution. IR (neat, cm⁻¹): 3407.53, 1652.66, 1616.81. UV-vis (CH₂Cl₂) λ_{max} = 727 nm (ε = 184,515 M⁻¹cm⁻¹), λ_{onset} = 757 nm.

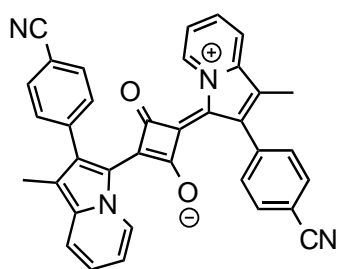
Synthetic Procedures: CNPh-In-SQ



4-(1-methylindolizin-2-yl)benzonitrile (26): To a flame dried round bottom flask equipped with a stir bar and a reflux condenser was added 4-(2-bromoacetyl)benzonitrile (0.5g, 2.23 mmol) and 2-ethylpyridine (0.256 mL, 2.23 mmol) and dissolved in 5 mL acetone. The mixture was then heated to 60°C and stirred for 16 hours to yield a white precipitate. The reaction mixture was

then cooled to room temperature, and the precipitate was filtered off, rinsed with cold acetone and dried. The solid was then dissolved in 5 mL H₂O with sodium bicarbonate (0.75 g, 8.93 mmol). The solution was heated to 100°C, during which a brown precipitate

formed. After 3 hours, the precipitate was extracted with 50 mL dichloromethane, washed 3 times with water, dried with magnesium sulfate and condensed to yield a dark brown solid (0.283 g, 54%). ^1H NMR (300 MHz, CDCl_3) δ 7.85 (d, J = 6.93 Hz, 1 H), δ 7.70 (d, J = 8.55 Hz, 2 H), δ 7.62 (d, J = 8.34 Hz, 2 H), δ 7.42 (s, 1 H), δ 7.34 (d, J = 9.03 Hz, 1 H), δ 6.65 (t, J = 6.00 Hz, 1 H), δ 6.46 (t, J = 6.66 Hz, 1 H), δ 2.43 (s, 1 H). ^{13}C NMR (300 MHz, CDCl_3) δ 141.07, 132.28, 131.42, 128.84, 127.03, 124.85, 119.34, 117.73, 116.93, 110.88, 110.24, 109.48, 105.69, 9.81. IR (neat, cm^{-1}): 3100, 2912, 2842, 2219.



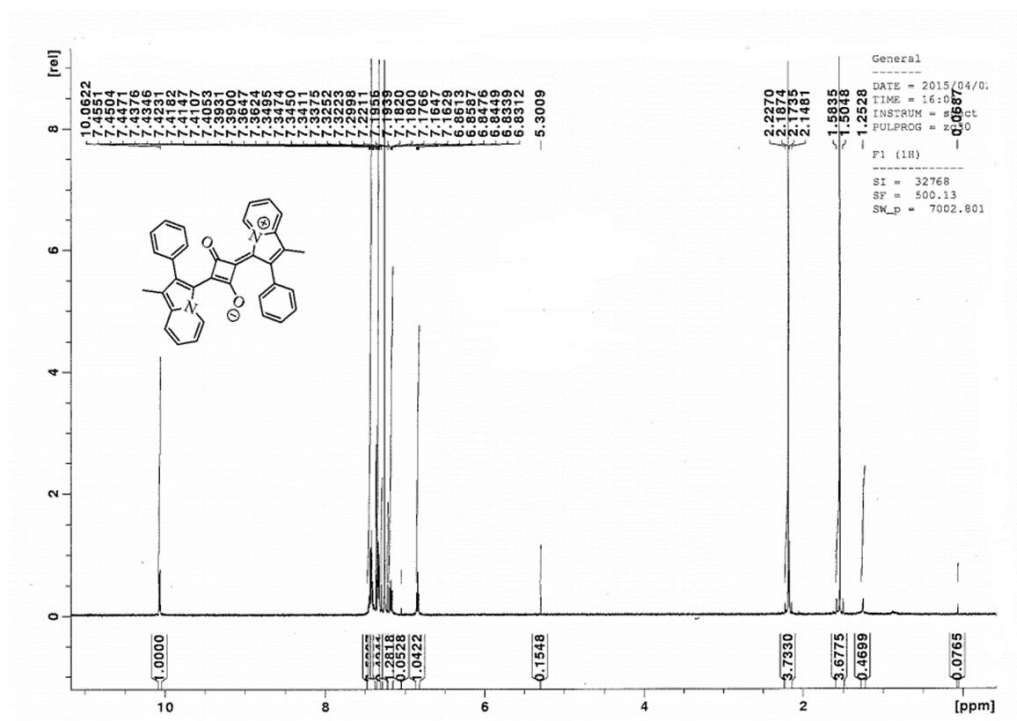
(Z)-4-(2-(4-cyanophenyl)-1-methyl-3H-indolizin-4-ium-3-ylidene)-2-(2-(4-cyanophenyl)-1-methylindolizin-3-yl)-3-oxocyclobut-1-en-1-olate (27): To a flame dried, N_2

flushed round bottom flask was added **(17)** (0.153 g, 0.659 mmol) and 3,4-dihydroxy-1,2-cyclobutanedione (0.037 g, 0.33 mmol), and flushed with N_2 for 10 minutes, then dissolved in 38 mL 1:1 toluene:n-butanol. The reaction mixture was heated to 130°C with a reflux condenser for 2.5 hours, during which a green solid precipitated. The precipitate was extracted with dichloromethane, then condensed. To purify, the solid was recrystallized in hexanes three times, then suspended in diethyl ether and centrifuged. The resulting supernatant was decanted off to yield a metallic green solid (0.23g, 46%). ^1H NMR (300 MHz, CDCl_3) δ 10.12 (d, J = 7.0 Hz, 2 H), δ 7.72 (d, J = 8.3 Hz, 4 H), δ 7.41 (d, J = 8.25, 6 H), δ 7.27 (t, J = 6.85 Hz, 2 H), δ 6.96 (t, J = 5.6 Hz, 2 H), δ 2.17 (s, 6 H). ^{13}C NMR will not dissolve into solution. IR (neat, cm^{-1}): 3390, 2913, 2846, 2373, 2346, 2217, 1604, 1596. UV-vis (CH_2Cl_2) λ_{max} = 723 nm (ϵ = 213,492 $\text{M}^{-1}\text{cm}^{-1}$), λ_{onset} = 753 nm.

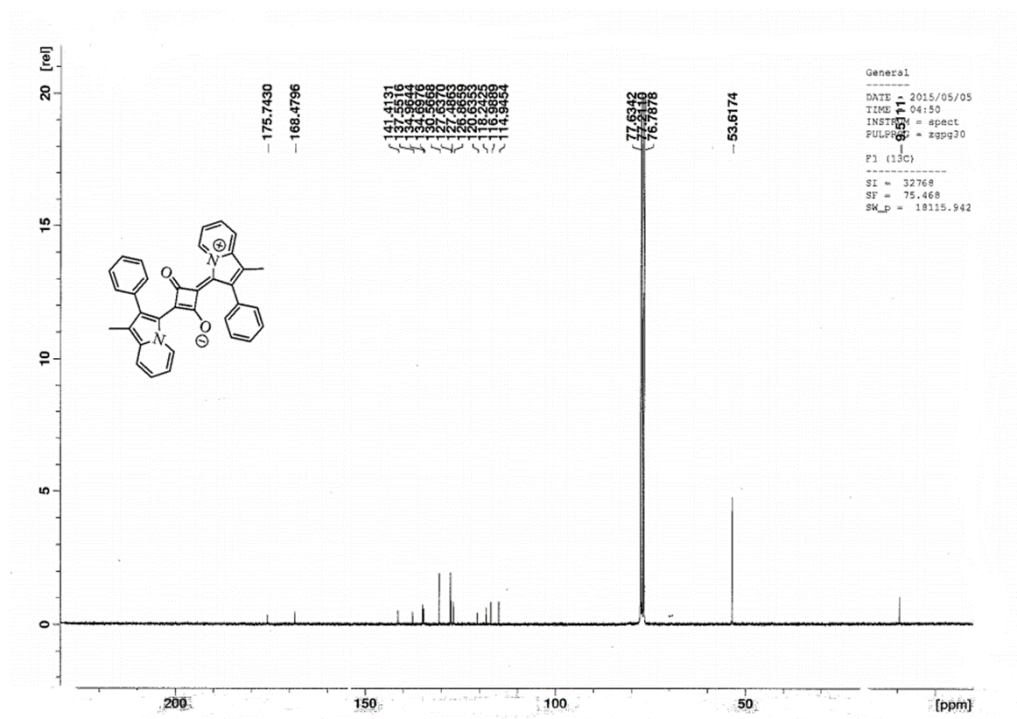
¹H NMR: 1,2-dimethylindolizine (1)



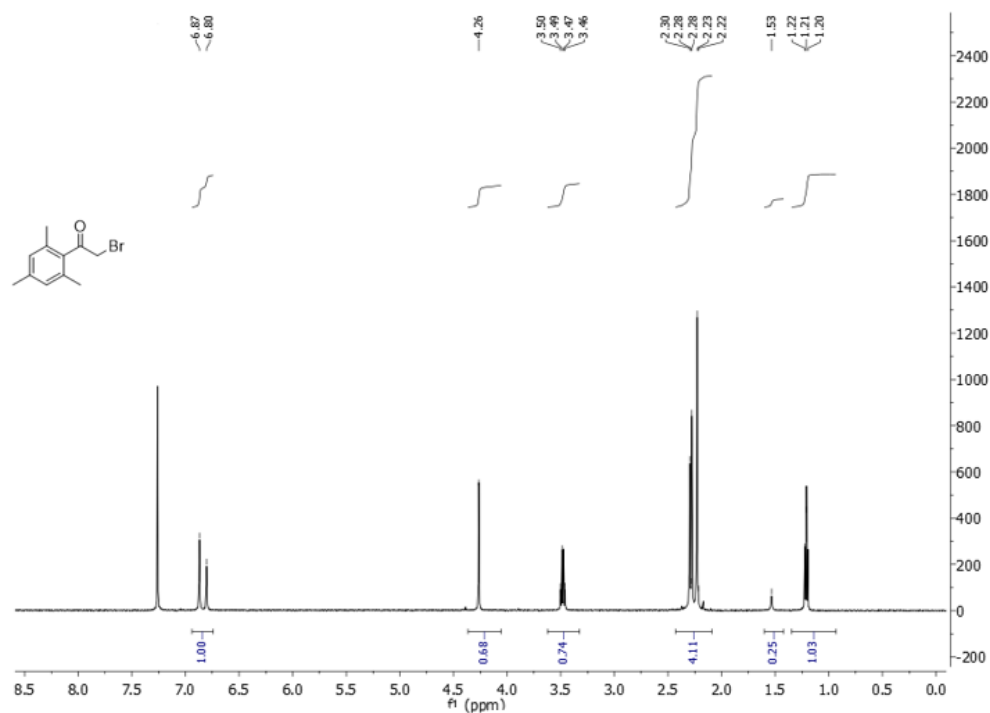
¹H NMR: (Z)-4-(1-methyl-2-phenyl-3H-indolizin-4-ium-3-ylidene)-2-(1-methyl-2-phenylindolizin-3-yl)-3-oxocyclobut-1-en-1-olate (5)



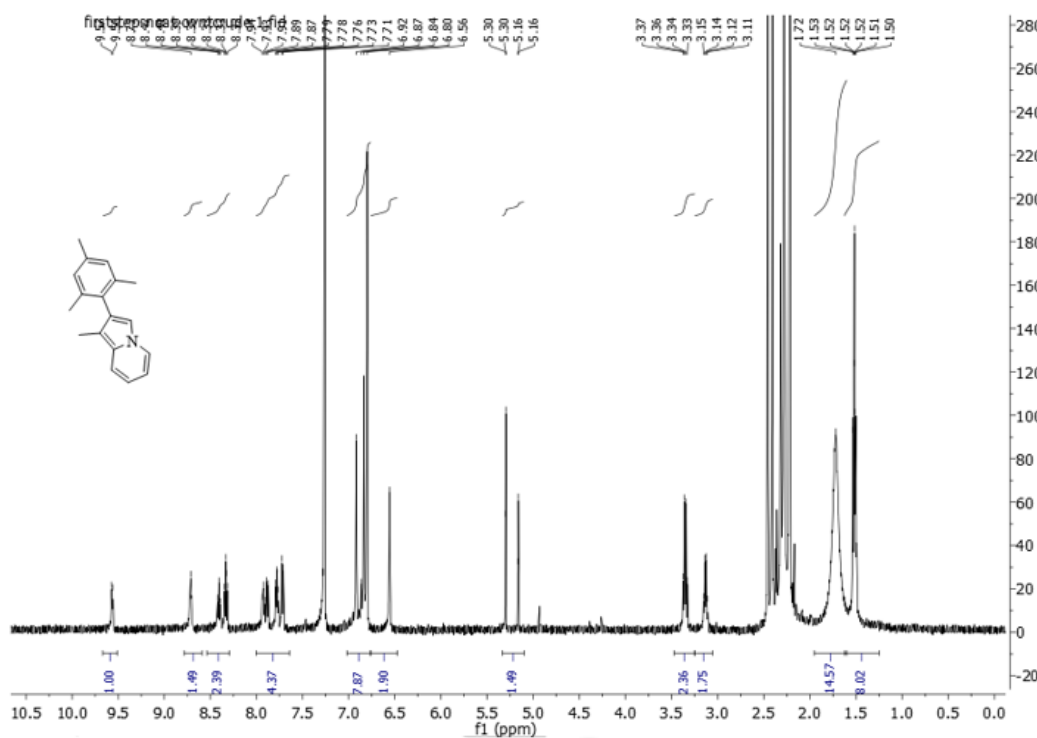
¹³C NMR: (Z)-4-(1-methyl-2-phenyl-3H-indolizin-4-ium-3-ylidene)-2-(1-methyl-2-phenylindolizin-3-yl)-3-oxocyclobut-1-en-1-olate (5)



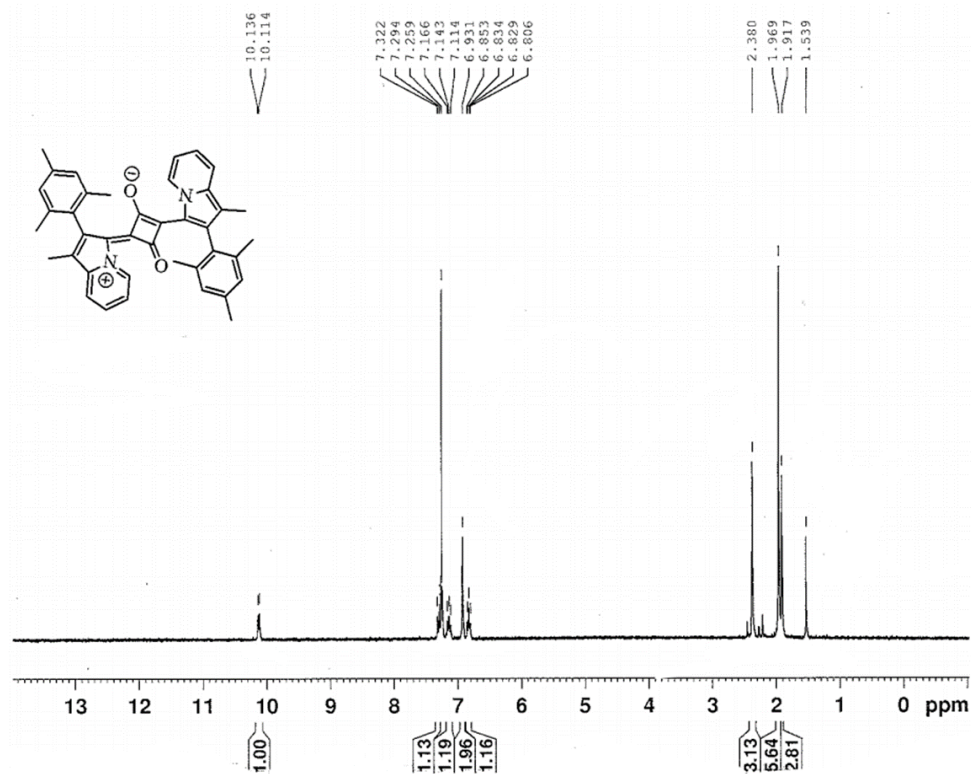
¹H NMR: 2-bromo-1-mesitylethanone (6)



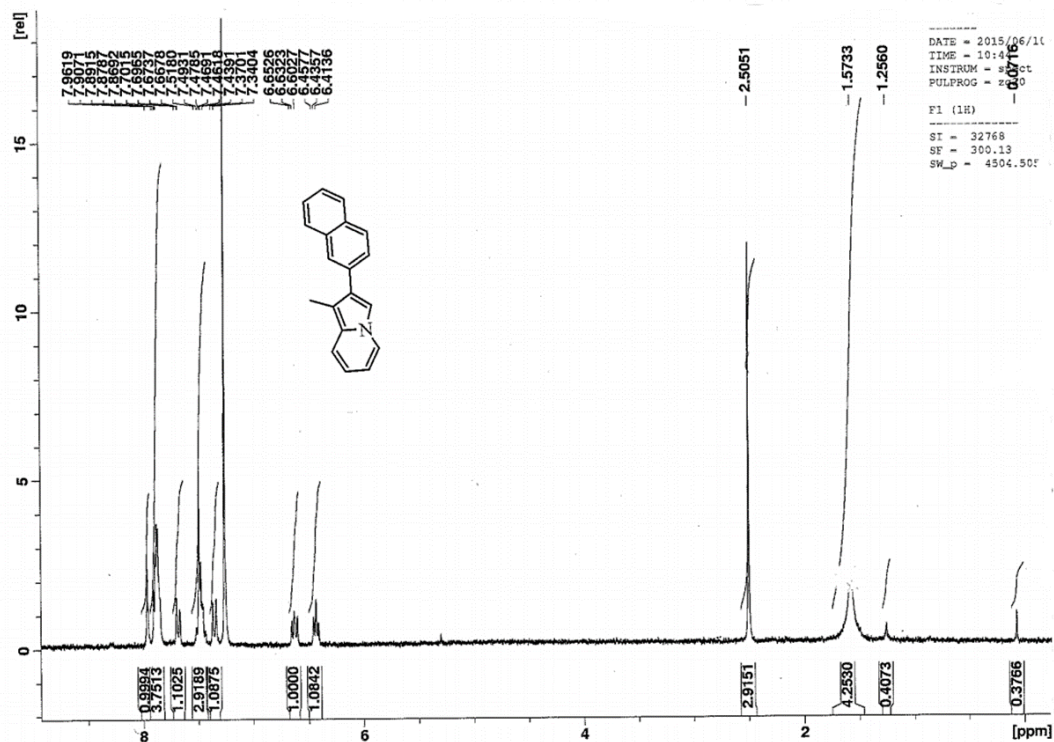
¹H NMR: 2-mesityl-1-methylindolizine (7)



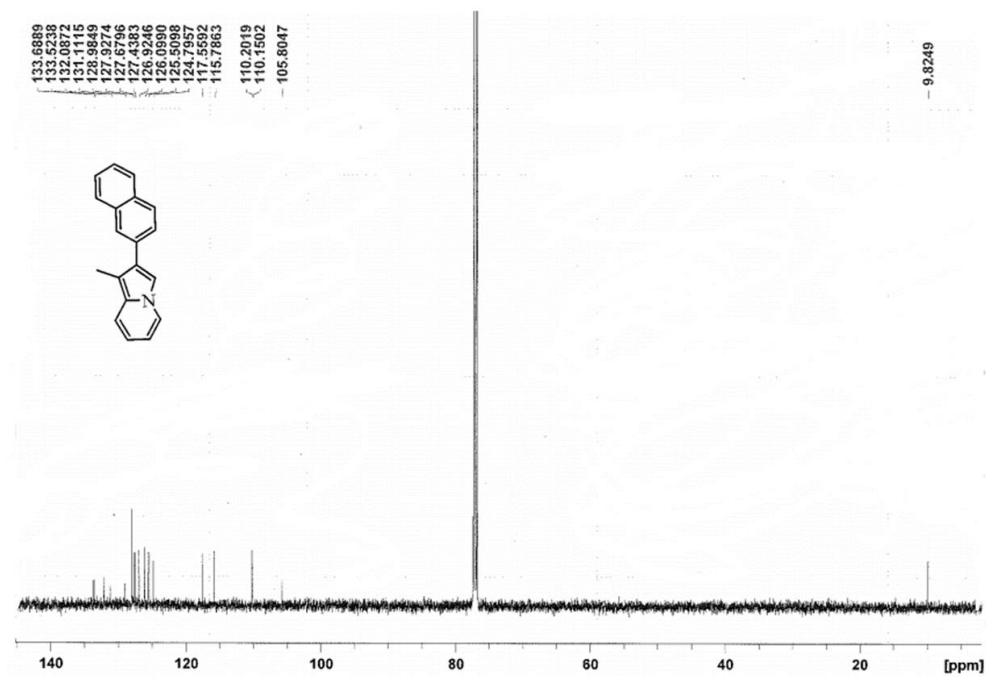
¹H NMR: (Z)-4-(2-mesityl-1-methyl-3H-indolizin-4-ium-3-ylidene)-2-(2-mesityl-1-methylindolizin-3-yl)-3-oxocyclobut-1-en-1-olate) (8)



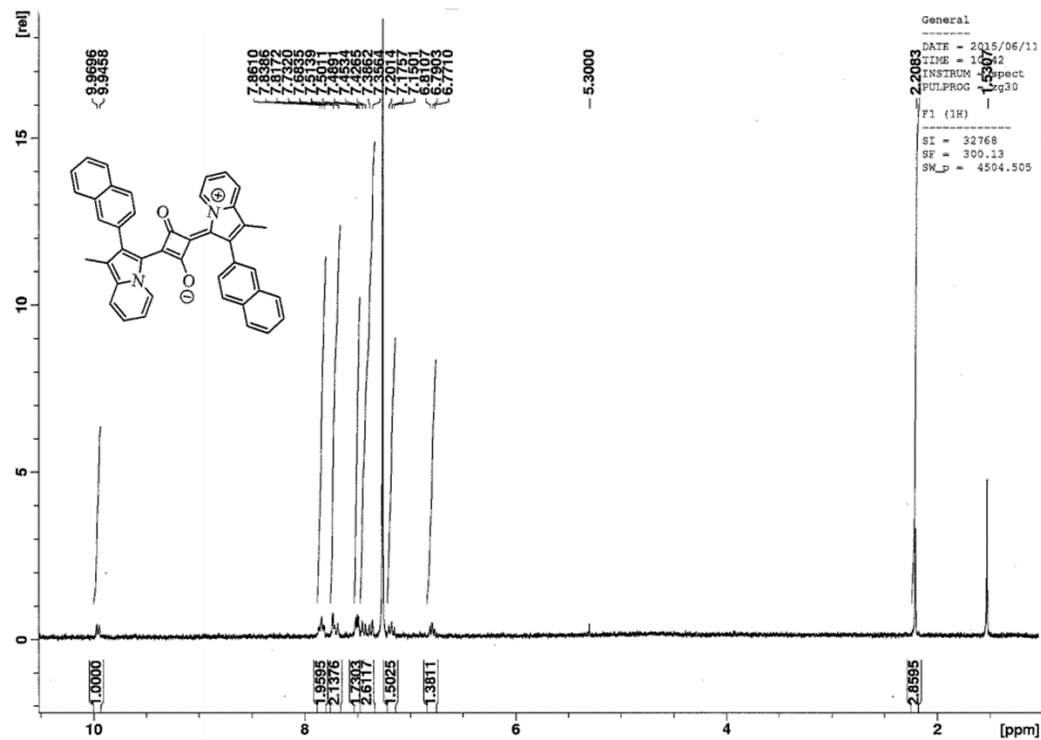
¹H NMR: 1-methyl-2-(naphthalene-2-yl)indolizine (9)

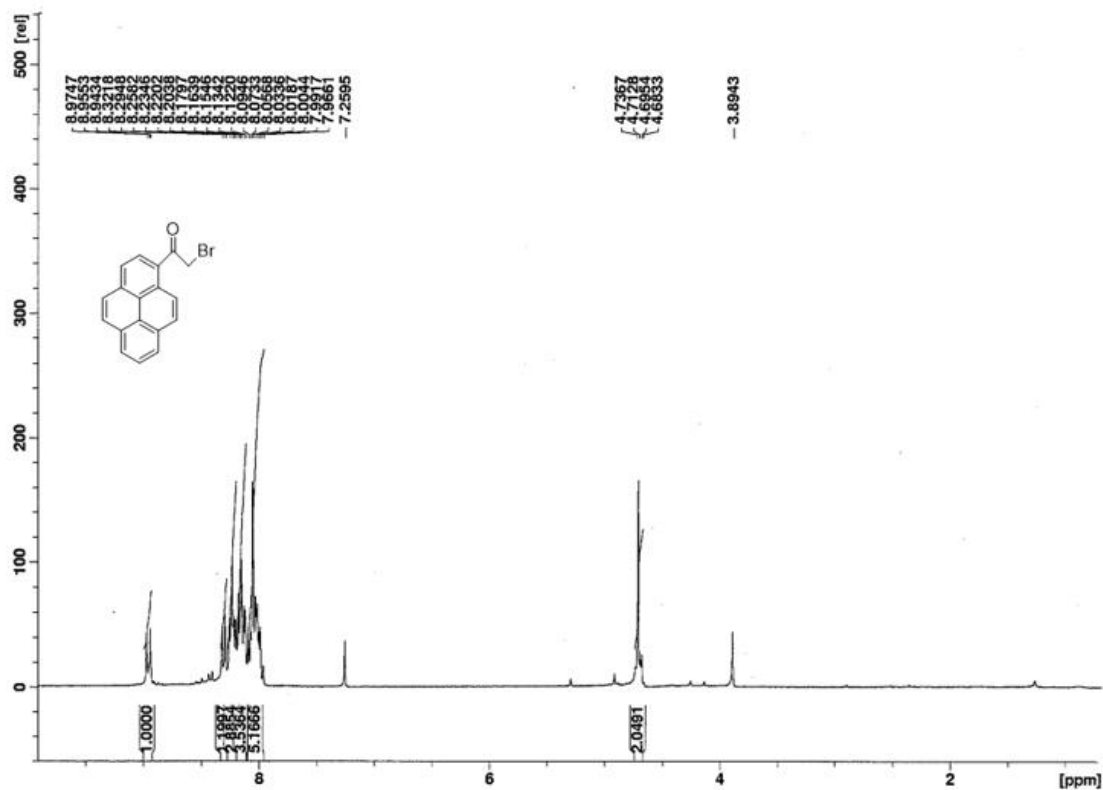


^{13}C NMR: 1-methyl-2-(naphthalene-2-yl)indolizine (9)

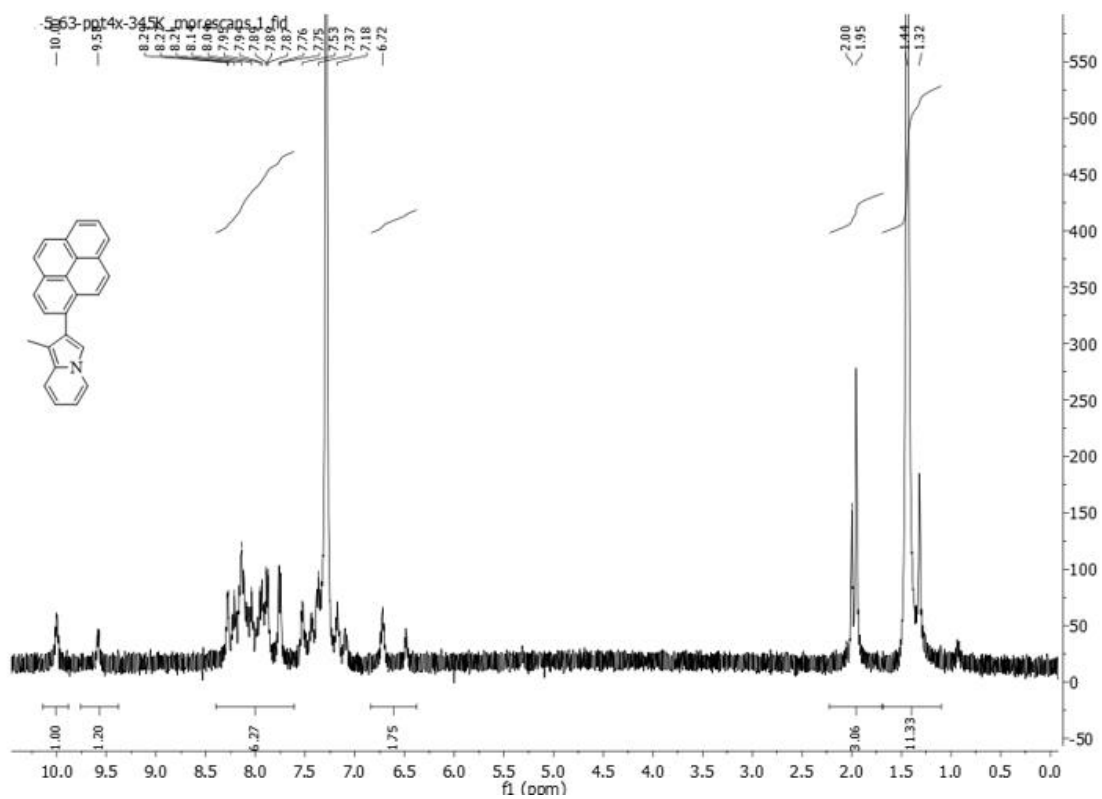


^1H NMR: (Z)-4-(1-methyl-2-(naphthalen-2-yl)-3H-indolizin-4-ium-3-ylidene)-2-(1-methyl-2-(naphthalene-2-yl)indolizin-3-yl)-3-oxocyclobut-1-en-1-olate (10)

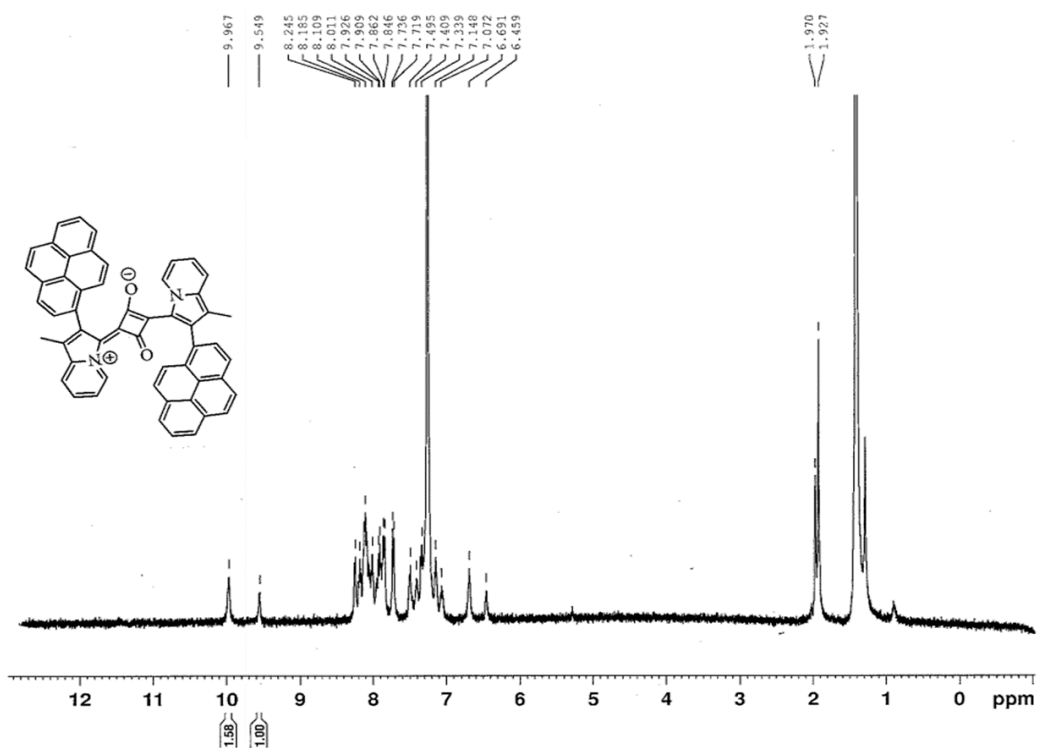


¹H NMR: 2-bromo-1-(pyren-4-yl)ethanone (11)

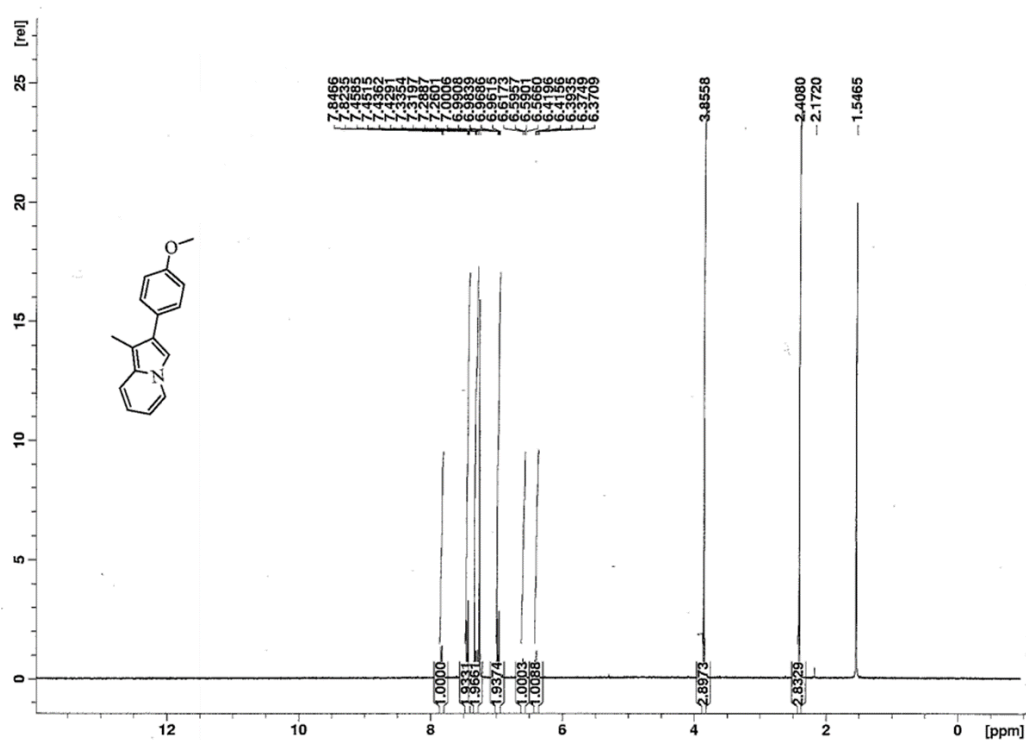
¹H NMR: 1-methyl-2-(pyren-2-yl)indolizine (12)



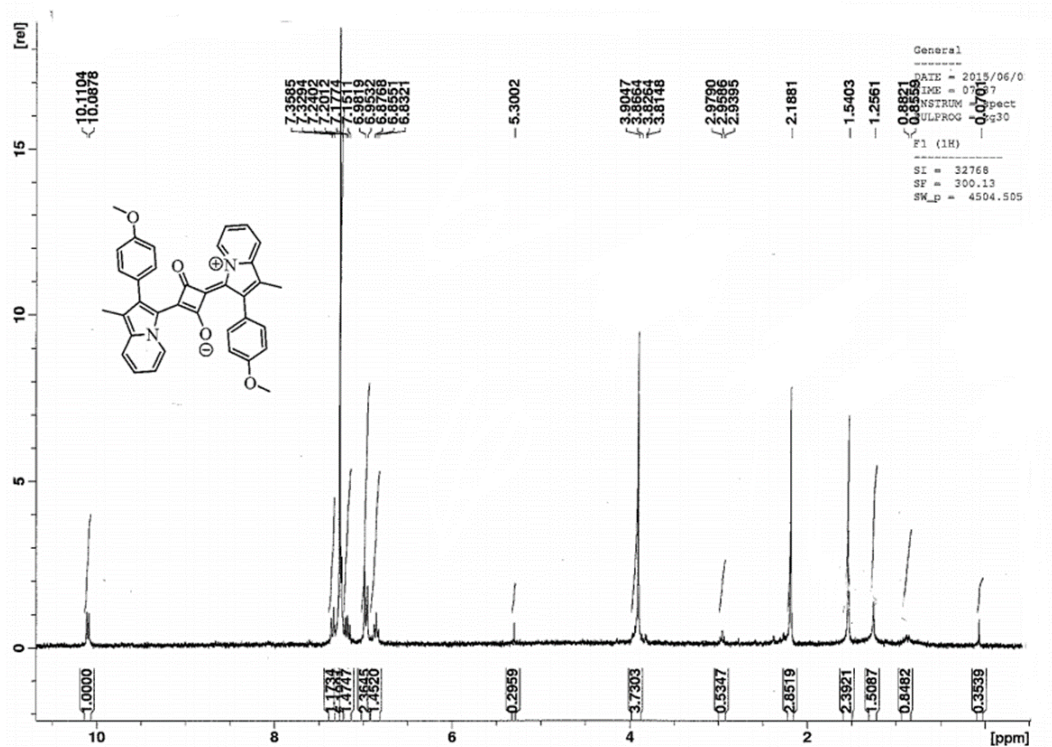
¹H NMR: (Z)-4-(1-methyl-2-(pyren-2-yl)-3H-indolizin-4-ium-3-ylidene)-2-(1-methyl-2-pyren-2-yl)indolizin-3-yl)-oxocyclobut-1-en-1-olate (13)



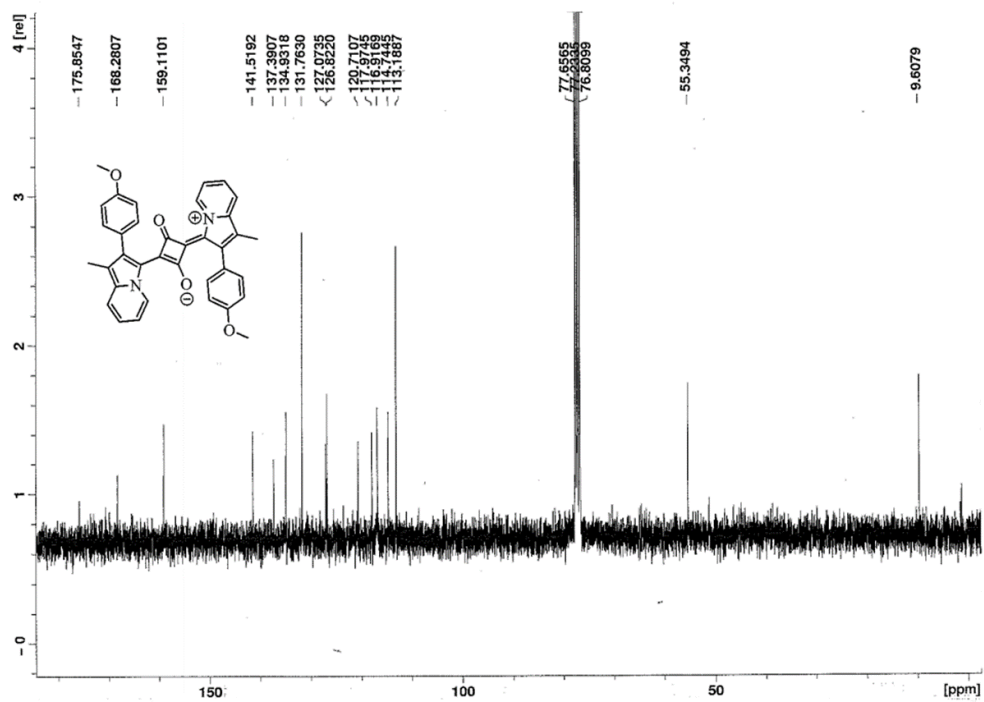
¹H NMR: 2-(4-methoxyphenyl)-1-methylindolizine (14):



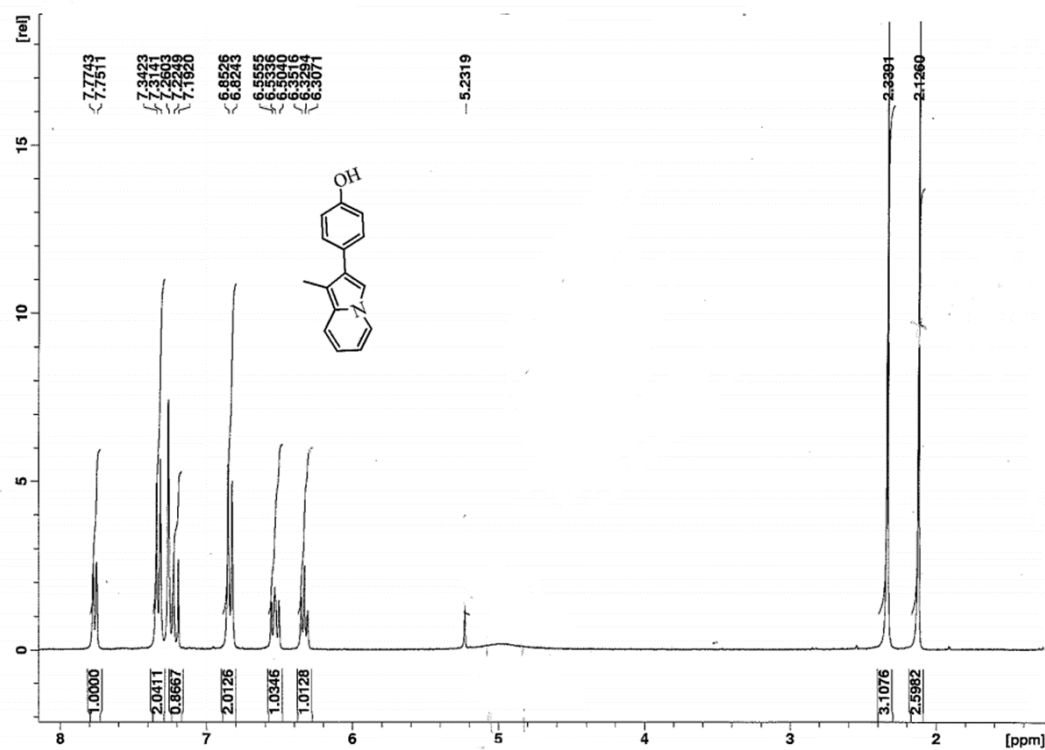
¹H NMR: (Z)-4-(2-(4-methoxyphenyl)-1-methyl-3H-indolizin-4-ium-3-ylidene)-2-(2-(4-methoxyphenyl)-1-methylindolizin-3-yl)-3-oxocyclobut-1-en-1-olate (15)



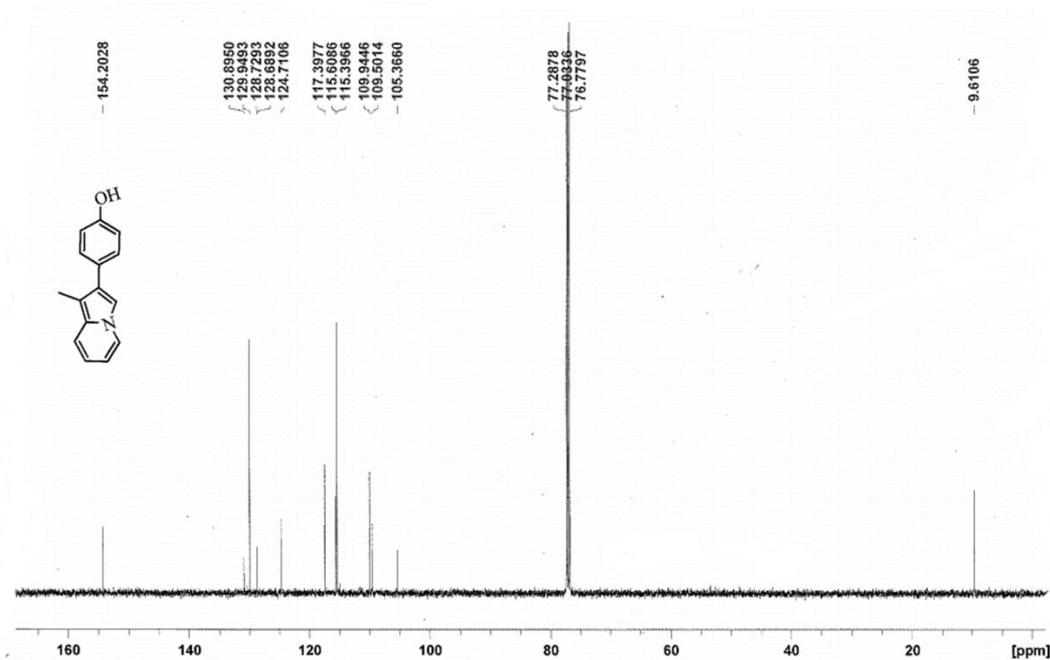
¹³C NMR: (Z)-4-(2-(4-methoxyphenyl)-1-methyl-3H-indolizin-4-ium-3-ylidene)-2-(2-(4-methoxyphenyl)-1-methylindolizin-3-yl)-3-oxocyclobut-1-en-1-olate (15)



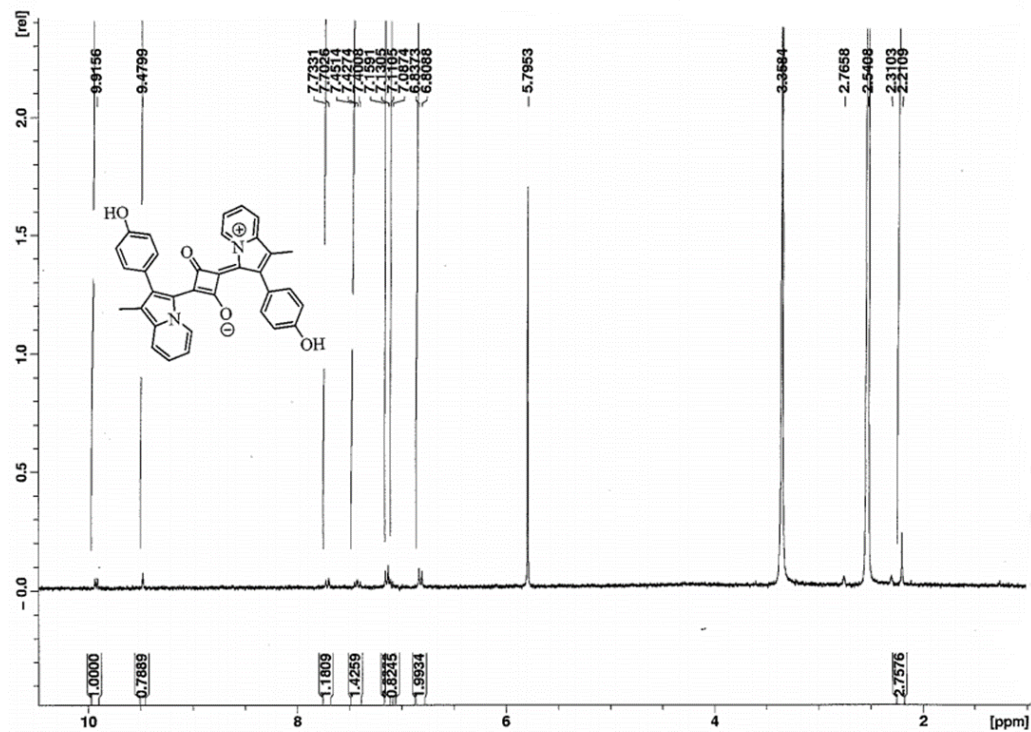
¹H NMR: 4-(1-methylindolizin-2-yl)phenol (16)



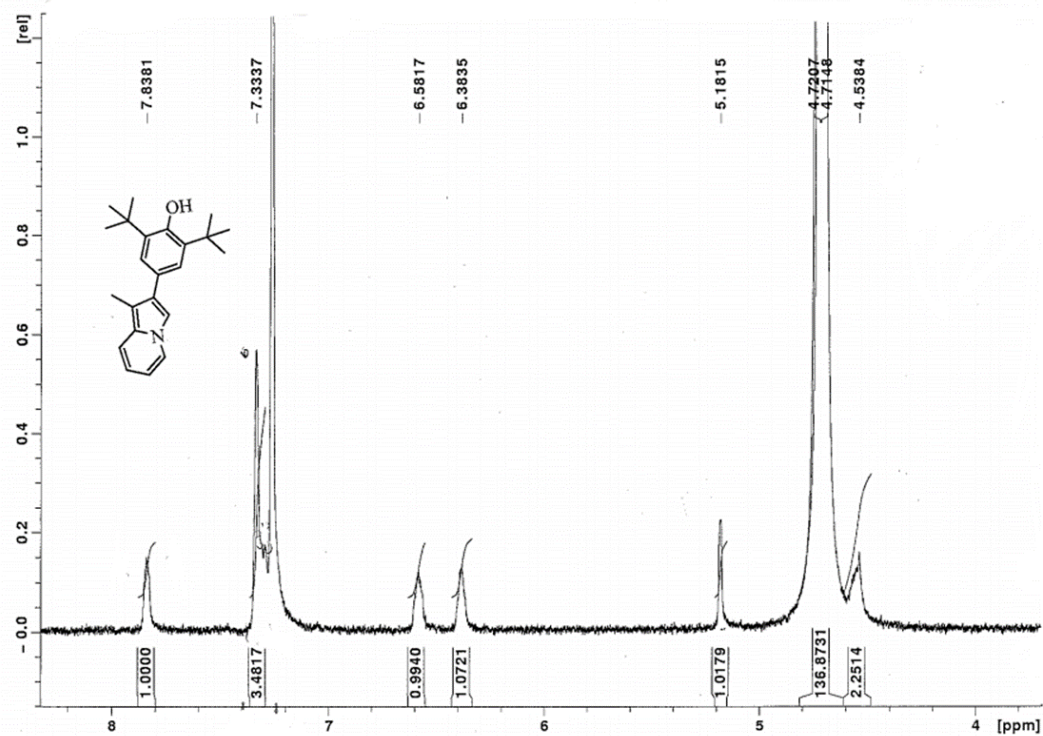
¹³C NMR: 4-(1-methylindolizin-2-yl)phenol (16)



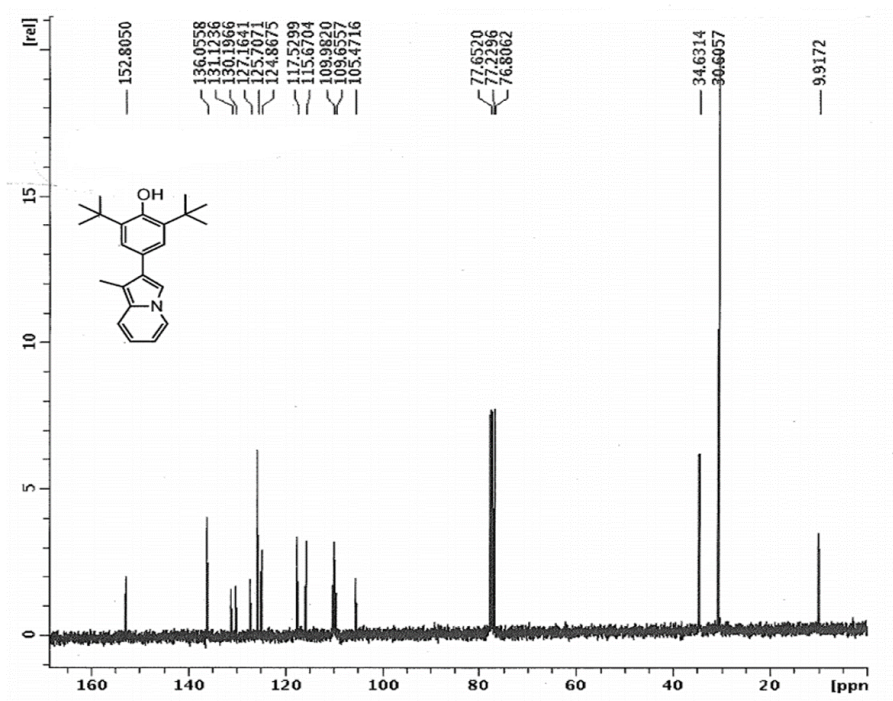
¹H NMR: (Z)-4-(2-(4-hydroxyphenyl)-1-methyl-3H-indolizin-4-ium-3-ylidene)-2-(2-(4-hydroxyphenyl)-1-methylindolizin-3-yl)-3-oxocyclobut-1-en-1-olate (17)



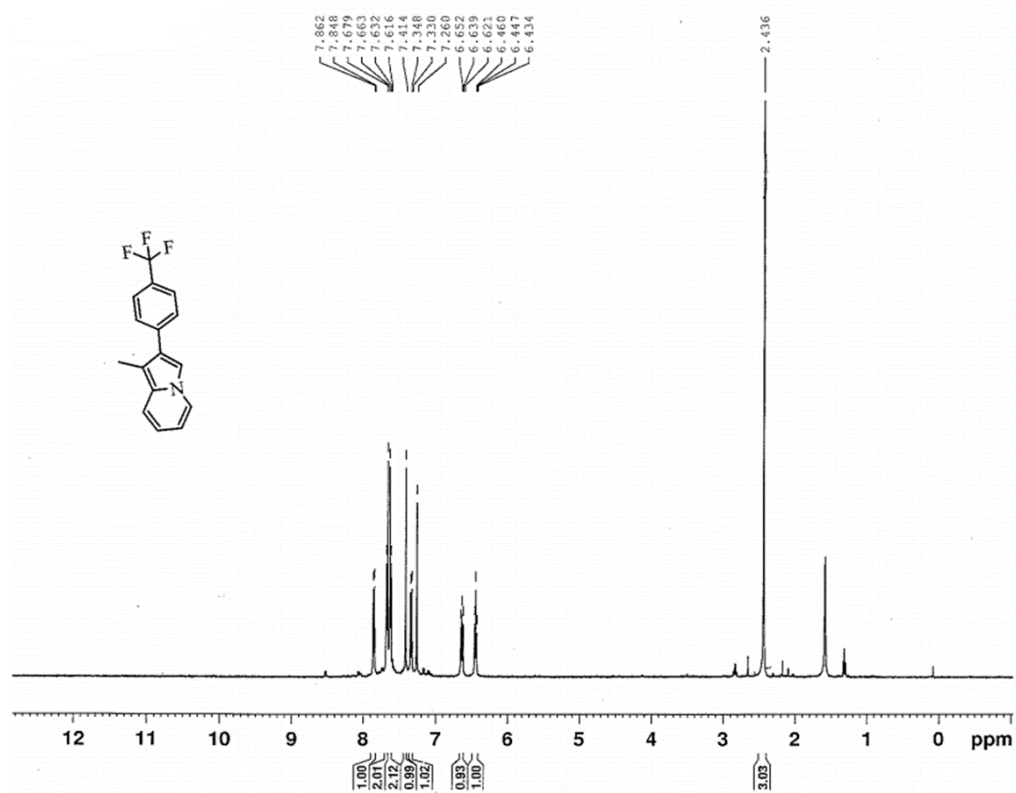
¹H NMR: 2,6-di-*tert*-butyl-4-(1-methylindolizin-2-yl)phenol (18)



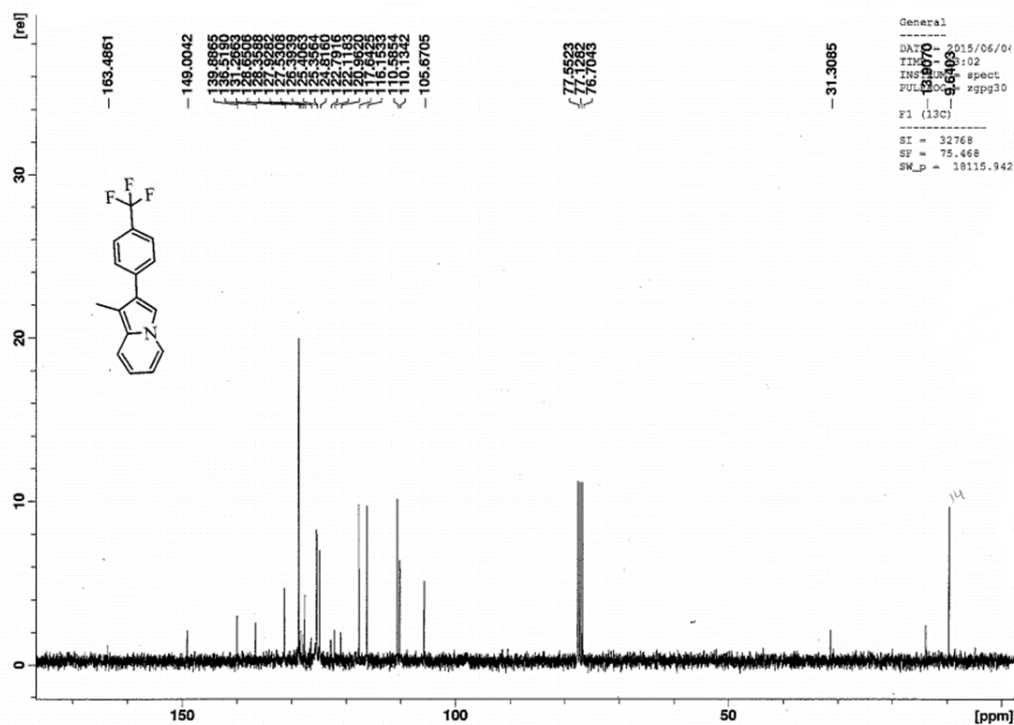
¹³C NMR: 2,6-di-*tert*-butyl-4-(1-methylindolizin-2-yl)phenol (18)



¹H NMR: 1-methyl-2-(4(trifluoromethyl)phenyl)indolizine (20)



¹³C NMR: 1-methyl-2-(4(trifluoromethyl)phenyl)indolizine (20)



Chemical structure: Cc1c[nH]c2ccc(cc12)-c3cc(C(F)(F)F)cc(F)c3

¹H NMR spectrum (CDCl₃) showing peaks and integration values:

Chemical Shift (ppm)	Integration
8.223	1.3223
7.9433	0.7133
7.7733	
7.5563	
7.7880	
7.4580	0.5667
7.3397	1.0068
7.2604	0.7886
6.6943	1.0000
6.6720	0.9661
6.6473	
6.4805	
6.4583	
5.3007	
2.3772	2.9772

Chemical structure: Cc1cc(C2=CC=CC=C2N2)cc(F)c(F)c12

Peak list (ppm): 149.19, 148.19, 147.19, 146.19, 145.19, 144.19, 143.19, 142.19, 141.19, 140.19, 139.19, 138.19, 137.19, 136.19, 135.19, 134.19, 133.19, 132.19, 131.19, 130.19, 129.19, 128.19, 127.19, 126.19, 125.19, 124.19, 123.19, 122.19, 121.19, 120.19, 119.19, 118.19, 117.19, 116.19, 115.19, 114.19, 113.19, 112.19, 111.19, 110.19, 109.19, 108.19, 107.19, 106.19, 105.19, 104.19, 103.19, 102.19, 101.19, 100.19, 99.19, 98.19, 97.19, 96.19, 95.19, 94.19, 93.19, 92.19, 91.19, 90.19, 89.19, 88.19, 87.19, 86.19, 85.19, 84.19, 83.19, 82.19, 81.19, 80.19, 79.19, 78.19, 77.19, 76.19, 75.19, 74.19, 73.19, 72.19, 71.19, 70.19, 69.19, 68.19, 67.19, 66.19, 65.19, 64.19, 63.19, 62.19, 61.19, 60.19, 59.19, 58.19, 57.19, 56.19, 55.19, 54.19, 53.19, 52.19, 51.19, 50.19, 49.19, 48.19, 47.19, 46.19, 45.19, 44.19, 43.19, 42.19, 41.19, 40.19, 39.19, 38.19, 37.19, 36.19, 35.19, 34.19, 33.19, 32.19, 31.19, 30.19, 29.19, 28.19, 27.19, 26.19, 25.19, 24.19, 23.19, 22.19, 21.19, 20.19, 19.19, 18.19, 17.19, 16.19, 15.19, 14.19, 13.19, 12.19, 11.19, 10.19, 9.19, 8.19, 7.19, 6.19, 5.19, 4.19, 3.19, 2.19, 1.19, 0.19.

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- PULPROG = zgpg30
- F1 (13C) = 101.25
- SI = 32768
- SF = 75.468
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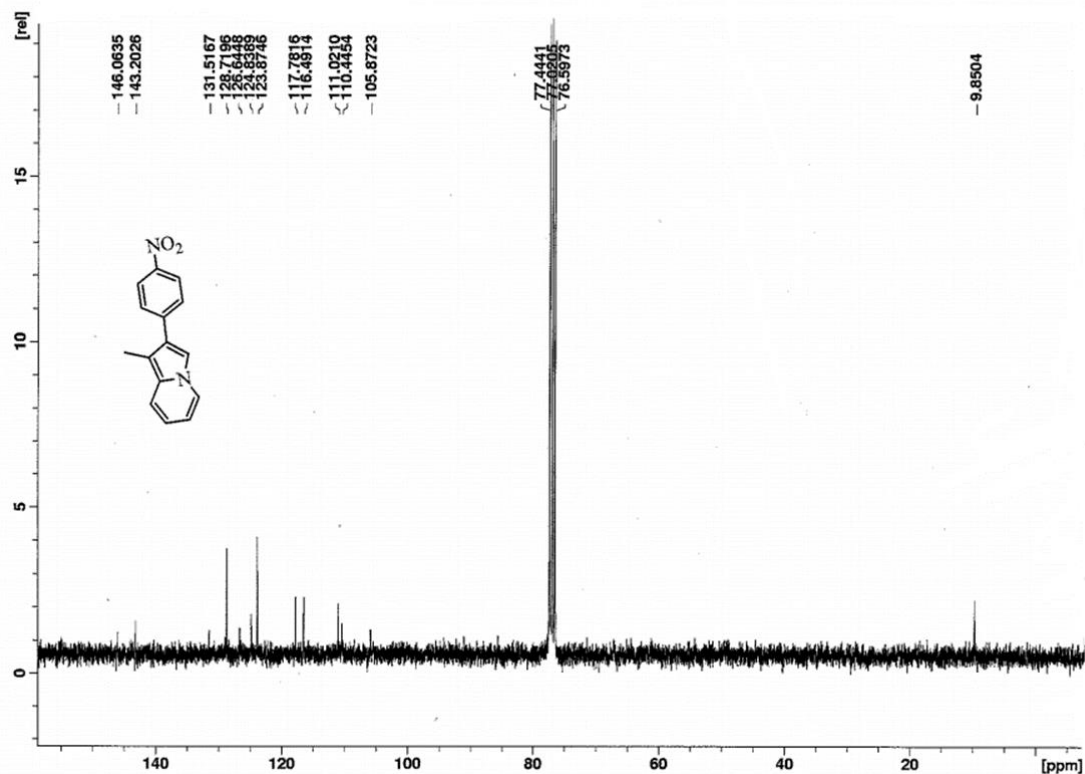
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Chemical structure: Cc1cc(C2=CC=C(C=C2)[N+](=O)[O-])cn1

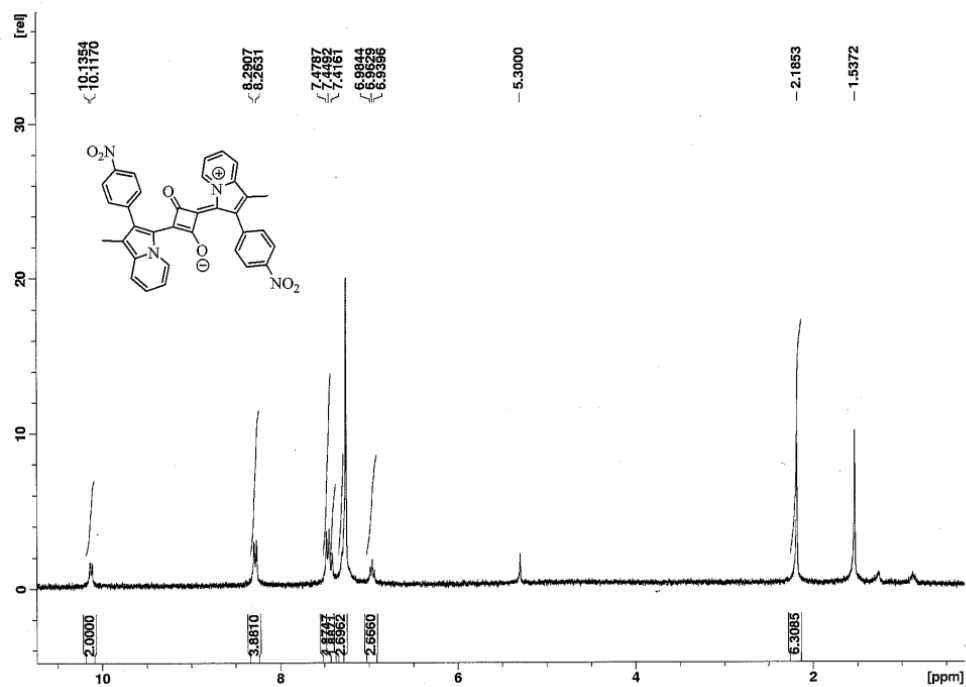
¹H NMR spectrum (DMSO-d₆) showing peaks and integration values:

Chemical Shift (ppm)	Integration
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8.2586	0.9226
7.8574	1.9725
7.8446	1.366
7.8362	1.1271
7.6123	1.0000
7.5813	0.9658
7.2597	
6.6798	
6.6574	
6.6372	
6.4925	
6.4709	
6.4498	
2.4578	2.7761
2.7609	
2.604	

¹³C NMR: 1-methyl-2-(4-nitrophenyl)indolizine (24)



¹H NMR: (Z)-4-(1-methyl-2-(4-nitrophenyl)indolizin-3-ylidene)-2-(1-methyl-2-(4-nitrophenyl)indolizin-3-yl)-3-oxocyclobut-1-en-1-olate (25)



¹H NMR: (Z)-4-(2-(4-cyanophenyl)-1-methyl-3H-indolizin-4-ium-3-ylidene)-2-(2-(4-cyanophenyl)-1-methylindolizin-3-yl)-3-oxocyclobut-1-en-1-olate (27)

